S1 in 76214

D26

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07K 5/02, 5/06, 5/08
A61K 37/02

A1

(11) International Publication Number: WO 93/14113

(43) International Publication Date: 22 July 1993 (22.07.93)

(21) International Application Number: PCT/JP93/00002

(22) International Filing Date: 4 January 1993 (04.01.93)

(30) Priority data:
9200535.4 10 January 1992 (10.01.92) GB

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

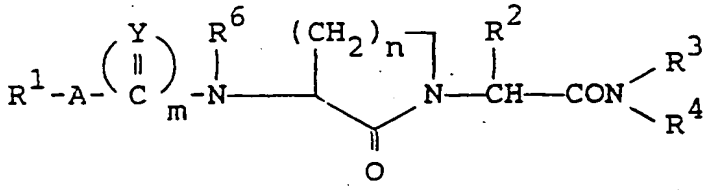
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MATSUO, Masaaki [JP/JP]; 4-12, Nakasakurazuka 5-chome, Toyonaka-shi, Osaka 560 (JP). HAGIWARA, Daijiro [JP/JP]; 20-11, Kindacho 2-chome, Moriguchi-shi, Osaka 570 (JP). MIYAKE, Hiroishi [JP/JP]; 86, Jodojinishidacho, Sakyo-ku, Kyoto-shi, Kyoto 606 (JP). IGARI, Norihiro [JP/JP]; 2-12-401, Ohsho-kita 4-chome, Amagasaki-shi, Hyogo 660 (JP). MURANO, Kenji [JP/JP]; 2-2-10, Midorigaoka, Ikeda-shi, Osaka 563 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
*With international search report.*

(54) Title: PEPTIDES WITH TACHYKININ ANTAGONIST ACTIVITY



(I)

(57) Abstract

The compound of formula (I) which is useful for treating or preventing Tachykinin-mediated diseases.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| AT | Austria | FR | France | MR | Mauritania |
| AU | Australia | GA | Gabon | MW | Malawi |
| BB | Barbados | GB | United Kingdom | NL | Netherlands |
| BE | Belgium | GN | Guinea | NO | Norway |
| BF | Burkina Faso | GR | Greece | NZ | New Zealand |
| BG | Bulgaria | HU | Hungary | PL | Poland |
| BJ | Benin | IE | Ireland | PT | Portugal |
| BR | Brazil | IT | Italy | RO | Romania |
| CA | Canada | JP | Japan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | | | SE | Sweden |
| CH | Switzerland | KR | Republic of Korea | SK | Slovak Republic |
| CI | Côte d'Ivoire | KZ | Kazakhstan | SN | Senegal |
| CM | Cameroon | LI | Liechtenstein | SU | Soviet Union |
| CS | Czechoslovakia | LK | Sri Lanka | TD | Chad |
| CZ | Czech Republic | LU | Luxembourg | TG | Togo |
| DE | Germany | MC | Monaco | UA | Ukraine |
| DK | Denmark | MG | Madagascar | US | United States of America |
| ES | Spain | ML | Mali | VN | Viet Nam |
| FI | Finland | MN | Mongolia | | |

# DESCRIPTION

## PEPTIDES WITH TACHYKININ ANTAGONIST ACTIVITY

### Technical Field

The present invention relates to new peptide compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new peptide compound and a pharmaceutically acceptable salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

### Disclosure of the Invention

Accordingly, one object of the present invention is to provide new and useful peptide compound and a pharmaceutically acceptable salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like.

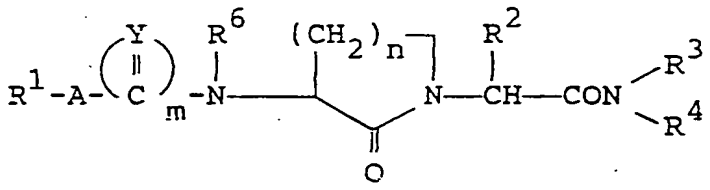
Another object of the present invention is to provide a process for the preparation of said peptide compound and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said peptide compound and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said peptide compound or a pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for

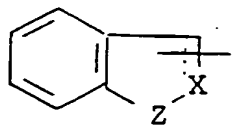
treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

The object compound of the present invention can be represented by the following general formula (I).



(I)

wherein $R^1$ is aryl, pyridyl, pyrrolyl, or a group of the formula :



wherein the line and the dotted line are a single bond or a double bond,
X is CH or N and
Z is -O-, -S- or -NH-,
each of which may have suitable substituent(s);

$R^2$ is ar(lower)alkyl which may have suitable substituent(s);

$R^3$ is lower alkyl which may have suitable

substituent(s);

$R^4$ is ar(lower)alkyl which may have suitable substituent(s);

$R^6$ is hydrogen or lower alkyl;

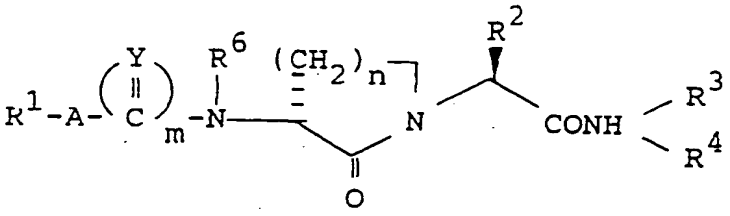
A is bond, lower alkylene or lower alkenylene;

Y is O or N-$R^7$ in which $R^7$ is hydrogen or lower alkyl;

m is 0 or 1; and

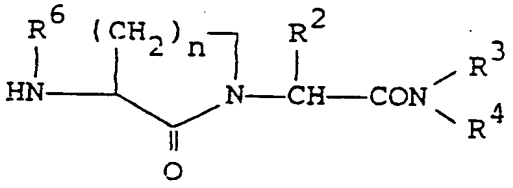
n is an integer of 0 to 2.

Preferred configuration of the compound (I) can be represented by the following formula.



According to the present invention, the new peptide compound (I) can be prepared by processes which are illustrated in the following schemes.

Process 1



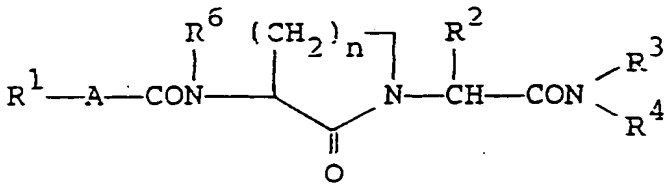
(II)

or its reactive derivative at the amino group, or a salt thereof

$R^1 - A - COOH$

(III)

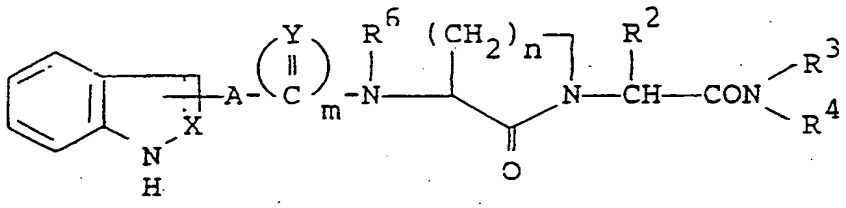
or its reactive derivative at the carboxy group, or a salt thereof



(I-a)

or a salt thereof

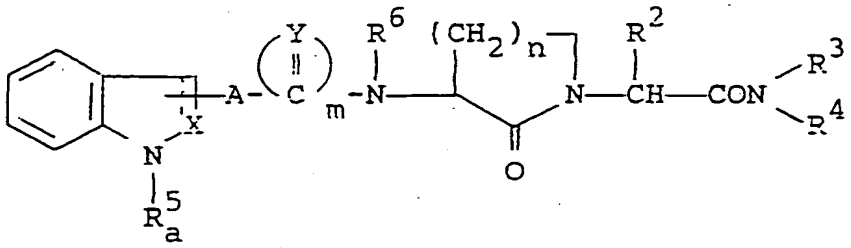
Process 2



Addition of Cyano(lower)-alkene

(I-b)

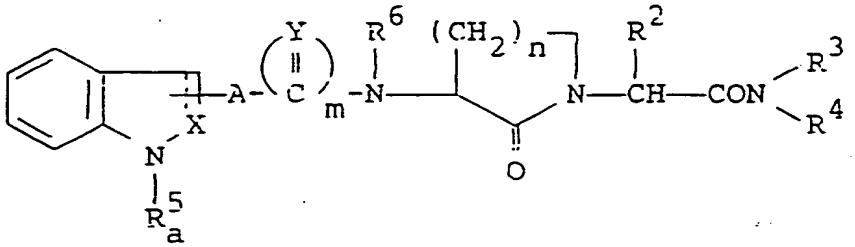
or a salt thereof



(I-c)

or a salt thereof

Process 3

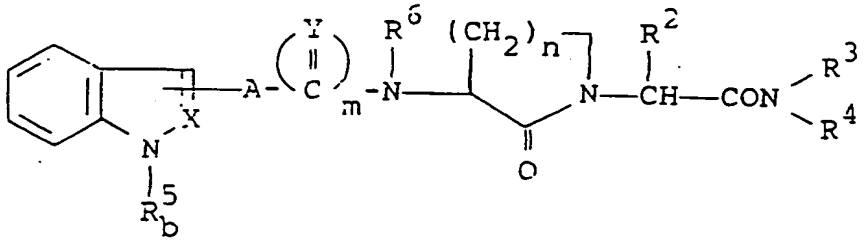


Ammonia

or a salt thereof

(I-c)

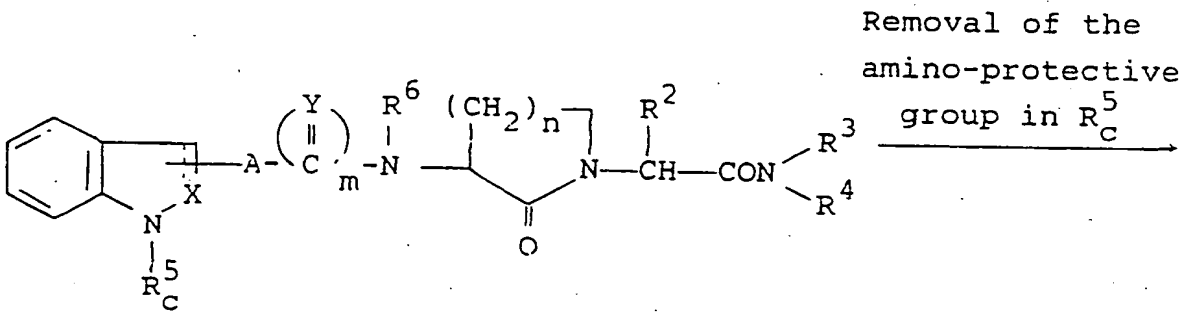
or a salt thereof



(I-d)

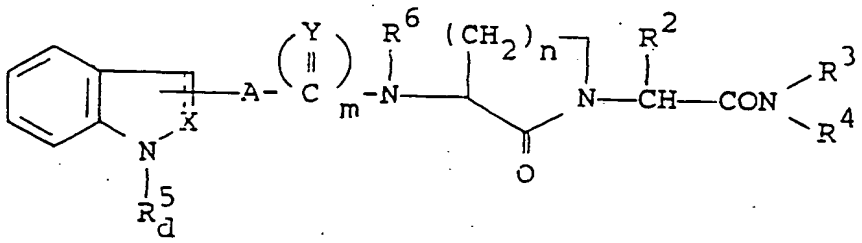
or a salt thereof

Process 4




(I-e)

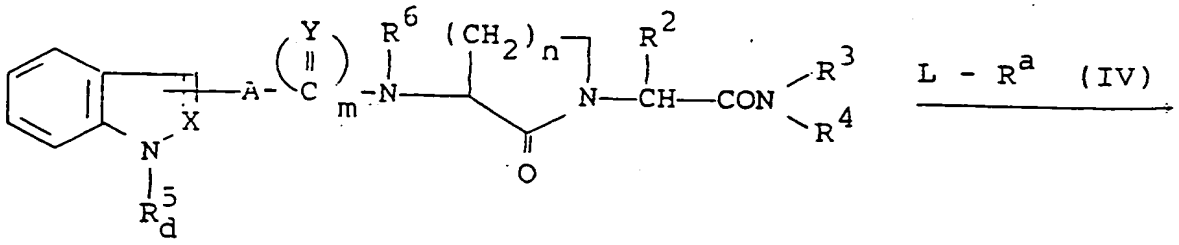
or a salt thereof



(I-f)

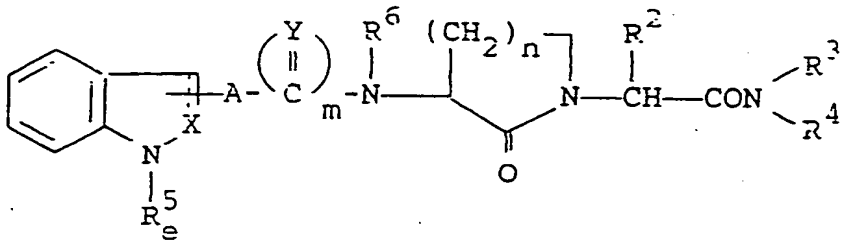
or a salt thereof

Process 5




(I-f)

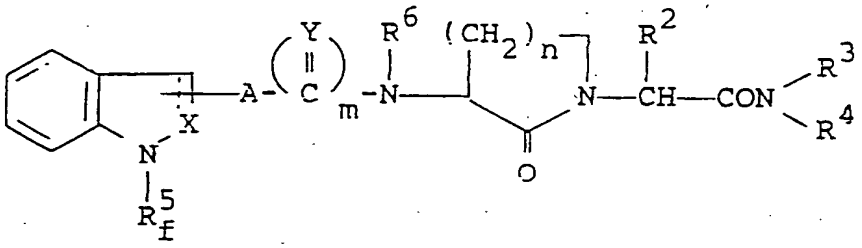
or a salt thereof



(I-g)

or a salt thereof

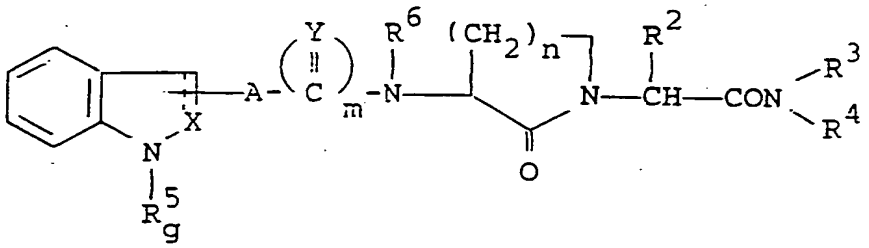
Process 6



lower alkylamine

(I-h)

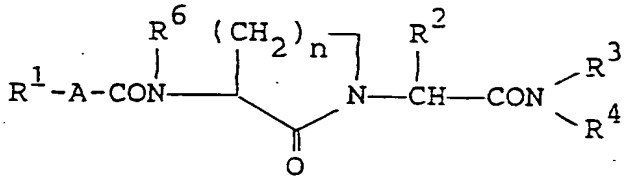
or a salt thereof



(I-i)

or a salt thereof

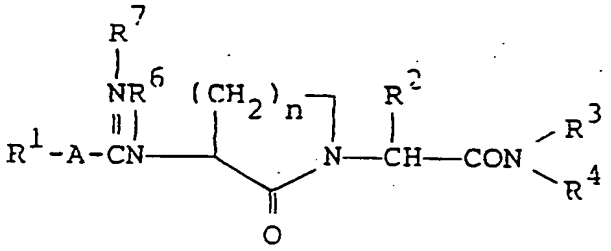
Process 7



$R^7NH_2$ (V) or a salt thereof

(I-a)

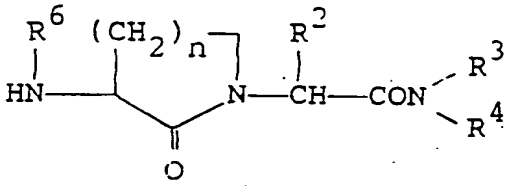
or a salt thereof



(I-j)

or a salt thereof

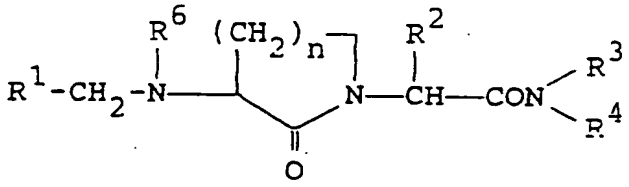
Process 8



Mannich reaction

(II)

or its reactive derivative at the amino group, or a salt thereof



(I-k)

or a salt thereof

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $R^7$, A, X, Y, m and n are each as defined above,

$R^5_{a_5}$ is cyano(lower)alkyl,

$R^5_b$ is amidino(lower)alkyl,

$R^5_{c5}$ is protected amino(lower)alkyl,
$R^5_d$ is amino(lower)alkyl,
$R^5_e$ is guanidino(lower)alkyl or [2-lower alkyl-3-cyanoisothioureido](lower)-alkyl,
$R^5_f$ is [2-lower alkyl-3-cyanoisothioureido](lower)-alkyl,
$R^5_g$ is [3-lower alkyl-2-cyanoguanidino](lower)-alkyl,
$R^a$ is amidino or (lower alkylthio)(cyanoimino)-methyl, and
L is a leaving group.

As to the starting compounds (II) and (III), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or a conventional manner.

Throughout the present specification, the amino acid, peptides, protective groups, condensing agents, etc. are expressed by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in common use in the field of this art.

Moreover, unless otherwise indicated, the amino acids and their residues when shown by such abbreviations are meant to be L-configured compounds and residues.

Suitable pharmaceutically acceptable salts of the starting and object compounds are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, phosphate, etc.), or a salt which an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a

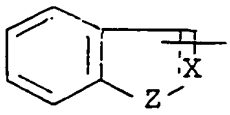
metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the variuos definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "aryl" may include phenyl, tolyl, xylyl, mesityl, cumenyl, naphthyl, and the like, in which the preferred one is $C_6$-$C_{10}$ aryl and the most preferred one is phenyl.

Suitable group represented by the formula :




may include indolyl (e.g. indol-1-yl, indol-2-yl, indol-3-yl, etc.), benzofuryl (e.g. benzofuran-2-yl, benzofuran-3-yl, etc.), benzothienyl (e.g. benzothien-2-yl, benzothien-3-yl, etc.), indazolyl (e.g. 1H-indazol-1-yl, 1H-indazol-3-yl, etc.), indolinyl (e.g. indolin-2-yl, indolin-3-yl, etc.), and the like, in which the preferred one is indolyl.

The aryl group and the group represented by the above formula may have one or more, preferably one to three suitable substituents such as lower alkyl (e.g. methyl,

ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, etc.); amino(lower)alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, etc.); protected amino(lower)alkyl, which means the above amino(lower)alkyl, in which the amino group is protected by a conventional amino-protective group used in the peptide chemistry such as acyl, for example, lower alkoxycarbonyl (e.g. tert-butoxycarbonyl, etc.); cyano(lower)alkyl (e.g. cyanomethyl, cyanoethyl, cyanopropyl, cyanobutyl, cyanopentyl, cyanohexyl, etc.); amidino(lower)alkyl (e.g. amidinomethyl, amidinoethyl, amidinopropyl, amidinobutyl, amidinopentyl, amidinohexyl, etc.); guanidino(lower)alkyl (e.g. guanidinomethyl, guanidinoethyl, guanidinopropyl, guanidinobutyl, guanidinopentyl, guanidinohexyl, etc.); [2-lower alkyl-3-cyanoisothioureido](lower)alkyl [e.g. 2-(3-cyano-2-methylisothioureido)ethyl, etc.]; [3-lower alkyl-2-cyanoguanidino](lower)alkyl [e.g. 2-(2-cyano-3-methylguanidino)ethyl, etc.]; mono or di(lower)alkylamino(lower)alkyl [e.g. 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 2- or 3-(dimethylamino)propyl, 2- or 3- or 4-(dimethylamino)butyl, etc.]; and the like.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene, ethylene or trimethylene.

Suitable "lower alkenylene" is one having 2 to 6 carbon atom(s) and may include vinylene, propenylene, and the like, in which the preferred one is vinylene.

Suitable "lower alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of this art such as lower alkyl as exemplified above, carboxy(lower)alkyl (e.g.

carboxymethyl, etc.), protected carboxy(lower)alkyl such as esterified carboxy(lower)alkyl, for example, lower alkoxycarbonyl(lower)alkyl (e.g. methoxycarbonylmethyl, etc.), carbamoyl(lower)alkyl (e.g. carbamoylmethyl, carbamoylethyl, etc.), lower alkylamino(lower)alkyl (e.g. dimethylaminomethyl, dimethylaminoethyl, etc.), hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, etc.), protected hydroxy(lower)alkyl such as acyloxy(lower)alkyl (e.g. acetyloxyethyl, etc.) halo(lower)alkyl (e.g. trifluoromethyl, etc.), and the like.

Suitable "ar(lower)alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as ar(lower)alkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, naphthylmethyl, tolylmethyl, xylylmethyl, mesitylmethyl, etc.), substituted ar(lower)alkyl (e.g., o-fluorobenzyl, m-fluorobenzyl, o-trifluoromethylbenzyl, etc.), and the like.

Suitable "cyano(lower)alkyl", "amidino(lower)alkyl", "protected amino(lower)alkyl", "amino(lower)alkyl", "guanidino(lower)alkyl", "[2-lower alkyl-3-cyanoisothioureido](lower)alkyl", "[2-lower alkyl-3-cyanoisothioureido](lower)alkyl" and [3-lower alkyl-2-cyanoguanidino](lower)alkyl may be the same as those given in the above.

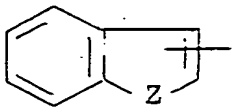
Suitable "(lower alkylthio)(cyanoimino)methyl" may include (methylthio)(cyanoimino)methyl, (ethylthio)(cyanoimino)methyl, and the like.

Suitable "leaving group" may include lower alkylthio (e.g. methylthio, ethylthio, etc.), substituted or unsubstituted pyrrol-1-yl (e.g. pyrrol-1-yl, 2,4-dimethylpyrrol-1-yl, etc.), and the like.

The preferred embodiments of the symbols $R^1$, $R^2$, $R^3$,

$R^4$, $R^6$, A, Y, m and n are as follows.

$R^1$ is aryl, preferably $C_6$-$C_{10}$ aryl (e.g. phenyl, etc.), pyridyl, pyrrolyl, or a group of the formula :



in which Z is -N- or -O-, wherein
$R^5$

$R^5$ is hydrogen;
lower alkyl (e.g. methyl, etc.);
di(lower)alkylamino(lower)alkyl [e.g. 2-(dimethylamino)ethyl, 3-(dimethylamino)-propyl, etc.];
amino(lower)alkyl (e.g. 2-aminoethyl, etc.);
protected amino(lower)alkyl, preferably acylamino(lower)alkyl such as lower alkoxycarbonylamino(lower)alkyl [e.g. 2-(tert-butoxycarbonylamino)ethyl, etc.];
cyano(lower)alkyl (e.g. 2-cyanoethyl, etc.);
amidino(lower)alkyl (e.g. 2-amidinoethyl, etc.);
guanidino(lower)alkyl (e.g. 2-guanidinoethyl, etc.);
[2-lower alkyl-3-cyanoisothioureido](lower)-alkyl [e.g. 2-(3-cyano-2-methyliso-thioureido)ethyl, etc.]; or
[3-lower alkyl-2-cyanoguanidino](lower)alkyl [e.g. 2-(2-cyano-3-methylguanidino)ethyl, etc.];

$R^2$ is ar(lower)alkyl, preferably $C_6$-$C_{10}$ ar(lower)alkyl such as phenyl(lower)alkyl (e.g. benzyl, etc.), mono or di(lower)alkylphenyl(lower)alkyl (e.g. 3-tolylmethyl,

3,4-xylylmethyl, etc.), naphthyl(lower)alkyl (e.g. 1-naphthylmethyl, 2-naphthylmethyl, etc.);

$R^3$ is lower alkyl (e.g. methyl, etc.);

$R^4$ is ar(lower)alkyl such as phenyl(lower)alkyl (e.g. benzyl, etc.);

$R^6$ is hydrogen or lower alkyl (e.g. methyl, etc.);

A is bond or lower alkenylene (e.g. vinylene, etc.);

Y is O or N-$R^7$ in which $R^7$ is hydrogen or lower alkyl (e.g. methyl, etc.);

m is 0 or 1; and

n is an integer of 1.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The compound (I-a) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsylil)acetamide, bis(trimethylsilyl)urea, and the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (II) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (III) may include conventional one which is used in the peptide chemistry such as an acid halide, an

acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt,

etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], or the like, and an acid addition salt as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, dichloromethane, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction. These conventional solvents may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as carbodiimide compound (e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-dimethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.), N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;

so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; and the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g. triethylamine, etc.), pyridine, N,N-di(lower)alkyl-1,3-propanediamine (e.g. N,N-dimethyl-1,3-propanediamine, etc.), N-(lower)alkylmorpholine (e.g. N-methylmorpholine, etc.), N,N-di(lower)alkylbenzylamine, and the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The compound (I-c) or a salt thereof can be prepared by subjecting the compound (I-b) or a salt thereof to addition reaction of cyano(lower)alkene.

Suitable "cyano(lower)alkene" may be acrylonitrile, and the like.

The present reaction is usually carried out in the presence of a base which is capable of leaving proton from the first position of an indole ring such as Triton B, and the like.

The present reaction is usually carried out in a solvent such as dioxane, dimethyl sulfoxide, dimethylformamide, methanol, ethanol, tetrahydrofuran, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process 3

The compound (I-d) or a salt thereof can be prepared by reacting the compound (I-c) or a salt thereof with ammonia or a salt thereof.

Suitable salt of ammonia may be an acid addition salt as exemplified for the compound (I).

This reaction can be carried out by a conventional method which is capable of converting a cyano group to an amidino group.

In this reaction, the compound (I-c) is preferably converted to its imido ether compound as the first step by alcohol (e.g. methanol, ethanol, etc.) in the presence of an acid (e.g. hydrogen chloride, etc.), and then the intermediary imido ether compound are transformed into the object compound (I-d).

This reaction is usually carried out in the presence of a conventional solvent such as methanol, ethanol or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process 4

The compound (I-f) or a salt thereof can be prepared by subjecting the compound (I-e) or a salt thereof to removal reaction of the amino-protective group.

In the present removal reaction, all conventional methods used in a removal reaction of an amino-protective group in the peptide chemistry, for example, hydrolysis, reduction, etc. are applicable. When the amino-protective group is an acyl, it can be removed by hydrolysis. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[5.4.0]undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrogen chloride, hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent (e.g. ethyl acetate, etc.), water, or a mixed solvent thereof.

The reaction temperature is not critical, and it may suitably be selected in accordance with the kind of the amino-protective group and the removal method.

The reduction elimination can be applied preferably for elimination of the protective group such as ar(lower)alkyl (e.g. benzyl, etc.), and the like.

The reduction method applicable for the removal reacting may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chromium compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium on carbon, etc.), and the like.

Process 5

The compound (I-g) or a salt thereof can be prepared by reacting the compound (I-f) or a salt thereof with the compound (IV).

The reaction can be carried out in the presence of a base as exemplified in Process 1.

This reaction is usually carried out in a conventional solvent such as dimethyl formamide, methanol, ethanol or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 6

The compound (I-i) or a salt thereof can be prepared by reacting the compound (I-h) or a salt thereof with lower alkylamine.

Suitable "lower alkylamine" used in this reaction may be $C_1$-$C_6$ alkylamine such as methylamine, ethylamine, propylamine, isopropylamine, butylamine, pentylamine, hexylamine, and the like.

This reaction is usually carried out in a conventional solvent such as N,N-dimethylformamide, methanol, ethanol, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 7

The compound (I-j) or a salt thereof can be prepared by reacting the compound (I-a) or a salt thereof with the compound (V) or a salt thereof.

The reaction can be carried out in the presence of a phosphorus compound (e.g. phosphorus pentachloride, etc.) and N,N-dimethylaniline.

This reaction is usually carried out in a conventional solvent such as ethanol, dimethylformamide, dichloromethane, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 8

The compound (I-k) or a salt thereof can be prepared by subjecting the compound (II) or its reactive derivative at the amino group or a salt thereof to Mannich reaction.

The reaction can be carried out in a conventional manner, that is, by the reaction of the compound (II) or its reactive derivative at the amino group or a salt thereof with formalin and a compound of the formula : $R^1$-H (preferably, indole), in which $R^1$ is as defined above, or a salt thereof in the presence of acid or base.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like, and in case the object compound can be isolated in a free form, it can be converted to its salt by a conventional method.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to

asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, expectoration, and the like;
opthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;
cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;
pains or aches (e.g. migraine, headache, toothache, cancerous pain, back pain, etc.); and the like.

Further, it is expected that the object compound (I) of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, and the like; epilepsy; spartic paralysis; pollakiuria; dementia; Alzheimer's diseases; schizophrenia; Huntington's chorea; carcinoid syndrome; and the like, and useful for immunosuppresive agent.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical

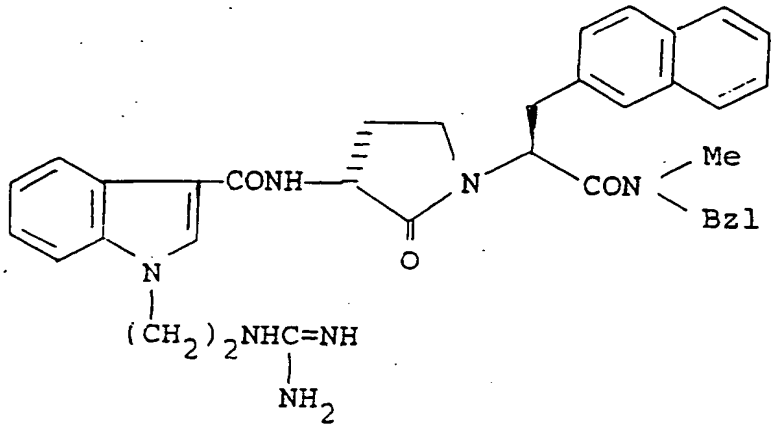
preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, topical or external administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, eye drops, solution, syrups, suspension, emulsion, or the like. If desired, there may be included in these preparation, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compound of the compound (I) is shown in the following.

(1) $^{3}$H-Substance P receptor binding

Test Compound :




Test Method :

(a) Crude lung membrane preparation

Male Hartly strain guinea pigs were sacrificed by decapitation. The trachea and lung were removed and homogenized in buffer (0.25 M sucrose, 50 mM Tris-HCl pH 7.5, 0.1 mM EDTA) by suing Polytoron (Kinematica). The homogenate was centrifuged (1000 xg, 10 min) to remove tissue clumps and the supernatant was centrifuges (14000 xg 20 min) to yield pellets. The pellets were resuspended in buffer (5 mM Tris-HCl pH 7.5), homogenized with a teflon homogenizer and centrifuged (14000 xg, 20 min) to yield pellets which were referred to as crude membrane fractions. The obtained pallets were stored at -70°C until use.

(b) $^{3}$H-Substance P binding to preparation membrane

Frozen crude membrane fractions were thawed and resuspended in Medium 1 (50 mM Tris-HCl pH 7.5, 5 mM $MnCl_2$, 0.02% BSA, 2 µg/ml chymostatin, 4 µg/ml leupeptin, 40 µg/ml bacitracin.) $^{3}$H-Substance P (1 nM) was incubated with 100 µl of the membrane preparation in Medium 1 at 4°C

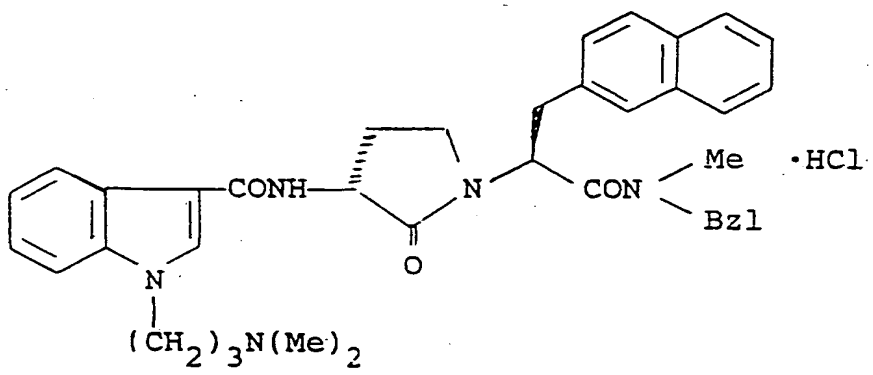
for 30 minutes in a final volume of 500 µl. At the end of the incubation period, reaction mixture was quickly filtered over a Whatman GF/B glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. The filters were then washed four times with 5 ml of the buffer (50 mM Tris-HCl, pH 7.5). The radioactivity was counted in 5 ml of Aquazol-2 in Packerd scintillation counter (Packerd TRI-CARB 4530).

Test Result :

$IC_{50}$ : 1.37 nM

(2) Effect of oral administration on Substance P induced bronchoedema in guinea-pigs

Test Compound :




Test Method :

Male Hartley guinea-pigs (300-400 g) were injected intravenously with Evans blue solution (20 mg/kg) containing Heparin (200 IU/kg) and Substance P (10 n mol/kg). Test compound (10 mg/kg) dissolved in dimethyl sulfoxide was orally given 30 minutes before this injection. After 10 minutes, the animals were sacrificed by blood-letting and the lungs were perfused with 50 ml of

saline. Trachea and stem bronchi were dissected out and dissolved in 0.5 ml of 1N KOH solution at 37°C for 6 hours. After the extraction with 4.5 ml of acetone-phosphate solution (0.6 $NaH_3PO_4$ : acetone = 5.13), the tissue Evans blue content was quantified colorimetrically at 620 nm.

Test Result :

Inhibition (%) : 95.7

The following examples are given for purpose of illustrating the present invention in detail.

In these examples, there are employed the following abbreviations in addition to the abbreviations adopted by the IUPAC-IUB.

| | | |
|---|---|---|
| Boc | : | t-butoxycarbonyl |
| Bzl | : | benzyl |
| Et | : | ethyl |
| HOBT | : | N-hydroxybenzotriazole |
| Me | : | methyl |
| 2Nal | : | (2-naphthyl)alanine |
| WSCD | : | 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide |

Preparation 1

To an ice-cooled solution of Boc-D-Met-OH (5.84 g), HCl·H-2Nal-N(Me)Bzl (8.32 g) and HOBT (3.16 g) in dichloromethane (100 ml) was added WSCD (4.27 ml). The solution was stirred at the same temperature for 2.5 hours and at room temperature for additional 2 hours. After concentration, the residue was extracted with ethyl acetate. The extract was washed successively with aqueous sodium hydrogencarbonate, water, 0.5N hydrochloric acid and saturated aqueous sodium chloride, and then dried over magnesium sulfate. The resultant solution was evaporated in vacuo, and the residue was crystallized from ethyl acetate and diisopropyl ether to give Boc-D-Met-2Nal-N(Me)Bzl (9.06 g).

mp : 126.0-127.0°C

IR (Nujol) : 3330, 1710, 1635, 1515 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.347 (9H, s); 1.45-1.70 (2H, m); 1.859, 1.902 (3H, s); 2.10-2.35 (2H, m); 2.803, 2.912 (3H, s); 2.90-3.25 (2H, m); 3.90-4.15 (1H, m); 4.379 (J=15.11Hz), 4.515 (J=18.40Hz), 4.600 (J=15.38Hz), 4.726 (J=16.62Hz)(2H, d); 4.95-5.25 (1H, m); 6.830 (J=14.62Hz), 6.887 (J=8.20Hz)(1H, d); 6.95-7.90 (12H, m); 8.383 (J=8.31Hz), 8.496 (J=8.50Hz)(1H, d)

Preparation 2

The following compounds were obtained by reacting the corresponding starting compounds with Boc-D-Met-OH or Boc-Met-OH in accordance with a similar manner to that of Preparation 1.

(1) Boc-D-Met-Phe-N(Me)(Bzl)

mp : 121.0°C

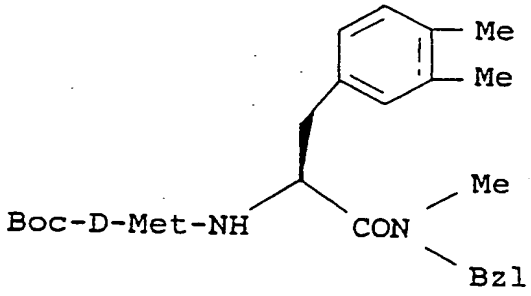
NMR (DMSO-$d_6$, δ) : 1.365 (9H, s); 1.50-1.78 (2H,

m); 1.989 (3H, s); 2.15-2.35 (2H, m); 2.792 and 2.896 (3H, s); 2.75-3.1 (2H, m); 3.95-4.1 (1H, m); 4.4-4.7 (2H, m); 4.85-5.1 (1H, m); 6.83 and 6.89 (1H, d, J=8.38Hz); 7.0-7.2 (10H, m); 8.32 and 8.42 (1H, d, J=8.61, 8.33Hz)

(2) Boc-Met-Phe-N(Me)(Bzl)

NMR (DMSO-$d_6$, δ) : 1.38 (9H, s); 1.6-1.8 (2H, m); 2.3-2.4 (2H, m); 2.73 and 2.80 (3H, s); 2.8-3.1 (2H, m); 3.8-4.1 (1H, m); 4.3-4.5 (2H, m); 4.9-5.1 (1H, m); 6.9-7.35 (11H, m); 8.1-8.25 (1H, m)

(3)



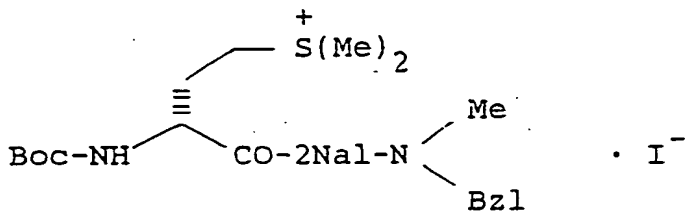

IR (Nujol) : 3350, 1682, 1659, 1641, 1519 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.359 (9H, s); 1.45-1.80 (2H, m); 1.96, 1.98 (3H, s); 2.00-2.35 (2H, m); 2.14, 2.17 (6H, s); 2.80-3.00 (2H, m); 2.80, 2.90 (3H, s); 3.90-4.10 (1H, m); 4.30-5.05 (3H, m); 6.65-7.40 (9H, m); 8.27 (J=8.32Hz), 8.38 (J=8.36Hz)(1H, d)

Preparation 3

To a solution of the product prepared in Preparation 1 (4.0 g) in ethyl acetate (45 ml) was added methyl iodide (20 ml) at room temperature. The mixture was stirred at the same temperature for 15 hours. The precipitated solid

from the solution was collected on sintered glass funnel and washed with ethyl acetate to give the following compound (3.70 g) as an amorphous solid.



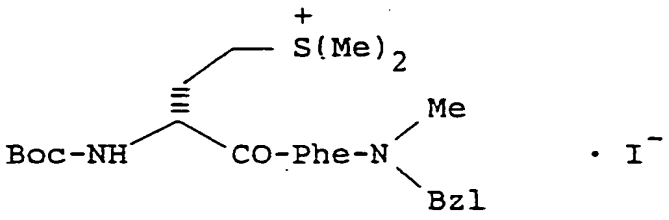
IR ($CHCl_3$) : 3440, 3300, 3000, 2940, 1710, 1642, 1492, 1454 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.358 (9H, s), 1.50-1.85 (2H, m), 2.729, 2.763, 2.800, 2.922 (9H, s); 3.00-3.20 (4H, m), 4.00-4.15 (1H, m); 4.30-4.70 (2H, m), 5.00-5.25 (1H, m), 7.009 (1H, d, J=5.02Hz); 7.05-7.95 (12H, m); 8.50-8.70 (1H, m)

Preparation 4

The following compounds were obtained by reacting the corresponding starting compounds with methyl iodide in accordance with a similar manner to that of Preparation 3.

(1)

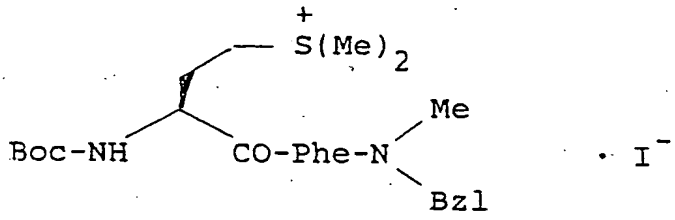


IR (Nujol) : 3200, 1714, 1675, 1630 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.375 (9H, s); 1.60-1.85 (2H, m); 2.15-2.35 (2H, m); 2.75-2.95 (2H, m); 2.795, 2.895 (3H, s); 2.866 (6H, s); 3.95-4.15 (1H, m);

4.35-4.7 (2H, m); 4.9-5.1 (1H, m); 7.07, 7.11 (1H, d, J=7.27Hz, J=7.27Hz); 7.20-7.38 (10H, m); 8.99, 8.58 (1H, d, J=8.66Hz, J=8.66Hz)

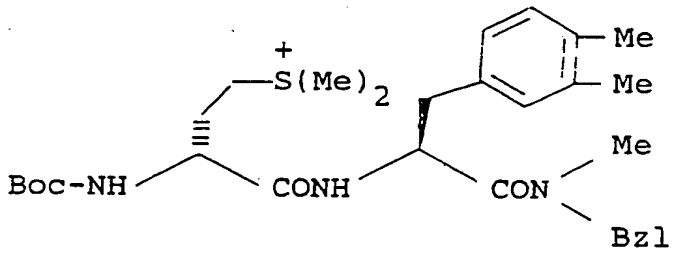
(2)




mp : 98-99°C

NMR (DMSO-$d_6$, δ) : 1.33 (9H, s); 1.9-2.05 (2H, m); 2.76 (2H, d, J=12Hz); 2.83 (6H, s); 3.2-3.3 (2H, m); 3.3-4.2 (1H, m); 4.4-4.6 (2H, m); 4.9-5.0 (1H, m); 7.0-7.4 (10H, m), 8.35 (1H, d, J=8Hz)

(3)

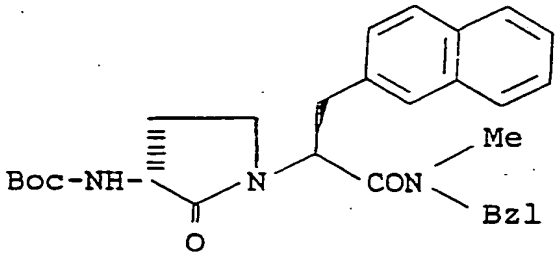



NMR (DMSO-$d_6$, δ) : 1.38 (9H, s); 1.55-2.35 (2H, m); 2.12, 2.17, 2.18 (6H, s); 2.60-3.30 (13H, m); 3.90-4.20 (1H, m); 4.30-4.75 (2H, m); 4.75-5.10 (1H, m); 6.70-7.40 (9H, m); 8.20-8.60 (1H, m)

Preparation 5

To an ice-cooled solution of the product obtained in Preparation 3 (1.5 g) in tetrahydrofuran (30 ml) and dimethylformamide (10 ml) was added 60% sodium hydride (173.5 mg) under nitrogen atmosphere. The mixture was

stirred for 45 minutes at the same temperature, and acetic acid (0.39 ml) was added thereto. After the mixture was stirred for 40 minutes, water (25 ml) was added to it at the same temperature. After concentration, the residue was extracted with ethyl acetate. The extract was washed successively with water, aqueous sodium hydrogencarbonate, water, 0.5N hydrochloric acid and saturated aqueous sodium chloride, and then dried over magnesium sulfate. The solution was concentrated in vacuo and the residue was crystallized from diethyl ether-diisopropyl ether to give the following compound (0.78 g).




mp : 140.5-143.5°C

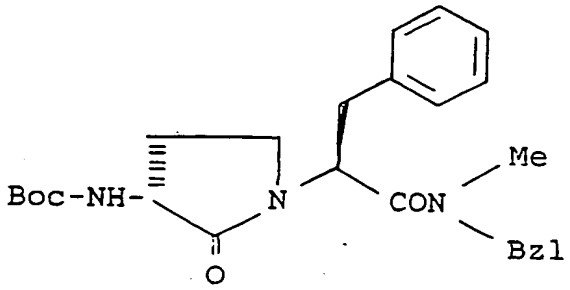
IR (Nujol) : 3303, 1722, 1680, 1650 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.362, 1.378 (9H, s); 1.65-1.95, 2.15-2.30 (2H, m); 2.732, 2.792 (3H, s); 3.15-3.60 (4H, m); 3.90-4.10 (1H, m); 4.10-4.40, 4.60-4.80 (2H, m); 5.203, 5.362 (1H, dd, J=8.08Hz, 6.70Hz); 6.70-7.95 (13H, m)

Preparation 6

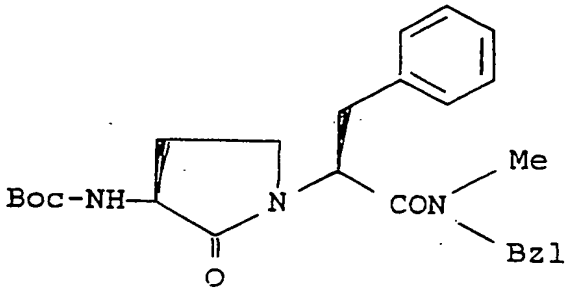
The following compounds were obtained by reacting the corresponding starting compounds with sodium hydride in accordance with a similar manner to that of Preparation 5.

(1)



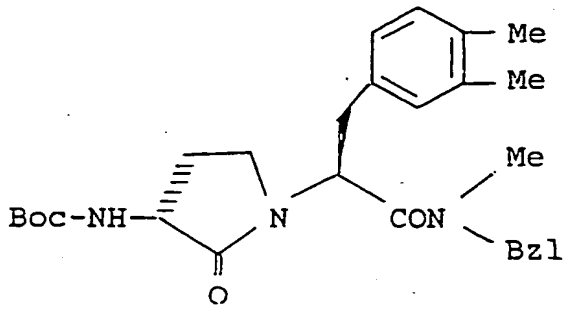

IR ($CHCl_3$) : 3340, 2990, 2950, 1695, 1645, 1495 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.371 (9H, s); 1.65-1.80, 2.15-2.35 (2H, m); 2.65-2.95 (2H, m); 2.772 (3H, s); 3.15-3.30, 3.40-3.55 (2H, m); 4.00-4.20 (1H, m); 4.25-4.40, 4.55-4.75 (2H, m); 5.00-5.25 (1H, m); 6.80-6.90 (1H, m); 6.90-7.40 (10H, m)

(2)




IR (Nujol) : 3440, 1720, 1690, 1655 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m); 2.15-2.3 (1H, m); 2.77, 2.87 (3H, s); 2.8-3.0 (1H, m); 3.1-3.4 (2H, m); 3.8-4.0 (1H, m); 4.92 (s), 4.23, 4.83 (ABq, J=16.9Hz)(2H); 5.1-5.3 (1H, m); 6.3-7.4 (10H, m)

(3)



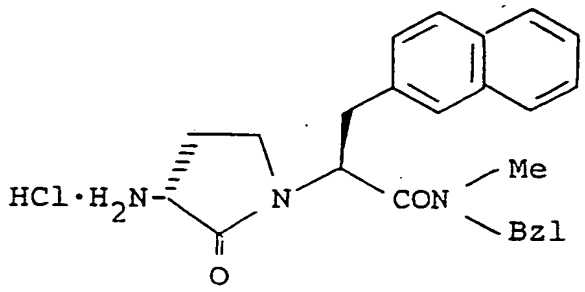

mp : 117-119°C

IR (Nujol) : 3260, 1700, 1665, 1610 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.38 (9H, s); 1.20-1.90 (2H, m); 2.13, 2.19 (6H, s); 2.73, 2.79 (3H, s); 2.60-3.55 (4H, m); 3.80-4.80 (3H, m); 4.95-5.25 (1H, m); 6.60-7.35 (9H, m)

Preparation 7

To an ice cooled solution of the product prepared in Preparation 5 (4.27 g) in dichloromethane (20 ml) was added 4N hydrogen chloride in dioxane (40 ml). The solution was stirred at the same temperature for 10 minutes and at room temperature for further 50 minutes. After concentration, ether was added to the residue, and the resulting precipitates were collected by filtration and dried to give the following compound (3.67 g) as an amorphous solid.



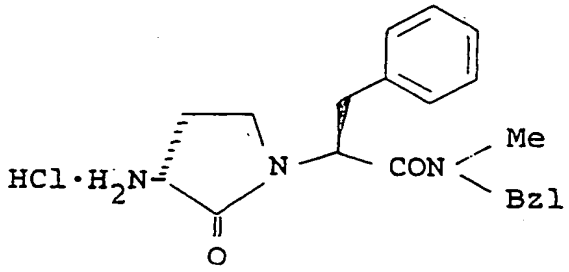
IR ($CHCl_3$) : 3430, 2930, 1690, 1640 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.80-2.15, 2.30-2.55 (2H, m); 2.747, 2.803 (3H, s); 2.95-3.85 (4H, m); 3.95-4.75 (3H, m); 5.250, 5.410 (1H, dd, J=6.20Hz, 8.82 Hz); 6.75-8.00 (12H, m); 8.621 (3H, s)

Preparation 8

The following compounds were obtained by reacting the corresponding starting compounds with hydrogen chloride in dioxane in accordance with a similar manner to that of Preparation 7.

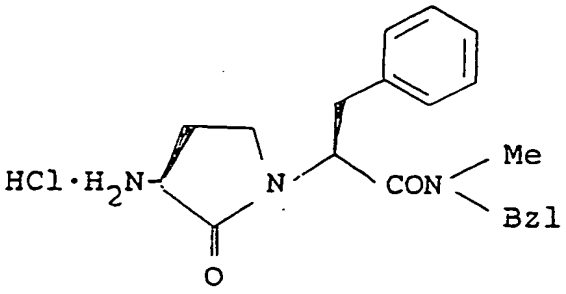
(1)




IR (Nujol) : 3400, 1693, 1640 $cm^{-1}$

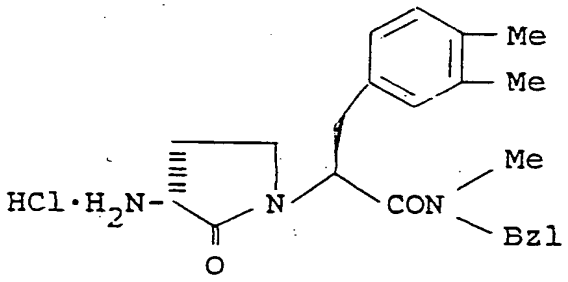
NMR (DMSO-$d_6$, δ) : 1.8-2.0, 2.3-2.55 (2H, m); 2.7-3.0 (2H, m); 2.7809 (3H, s); 3.2-3.4 (2H, m); 3.5-3.8 (2H, m); 4.0-4.1 (1H, t, J=8Hz); 4.2-4.8 (2H, m); 5.0-5.3 (1H, m); 6.8-7.4 (10H, m); 8.6476 (2H, s)

(2)



NMR (DMSO-$d_6$, δ) : 1.9-2.2 (1H, m); 2.35-2.5 (1H, m); 2.88 and 2.93 (3H, s); 2.8-3.25 (2H, m); 3.35-3.6 (2H, m); 3.78 (1H, q, J=8.7Hz); 4.32, 4.78 (ABq, J=16.8Hz) / 4.38, 4.61 (ABq, J=14.8Hz) } (2H); 5.11 (t, J=7.4Hz) / 5.25 (t, J=7.4Hz) } (1H); 6.9-7.4 (11H, m); 8.71 (3H, s)

(3)




IR ($CHCl_3$) : 3450, 2940, 1694, 1645 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.14, 2.18, 2.20 (6H, s); 1.80-2.50 (2H, m); 2.75, 2.80 (3H, s); 2.55-3.45 (2H, m); 3.10-3.70 (2H, m); 3.70-4.15 (1H, m); 4.15-4.75 (2H, m); 5.00-5.25 (1H, m); 6.75-7.30 (8H, m); 8.59 (3H, br s)

Preparation 9

To an ice-cooled solution of methyl indole-3-carboxylate (25 g) and 2-(N,N-dimethylamino)ethyl chloride hydrochloride (20.56 g) in dimethylformamide (500 ml) was added sodium hydride (60% in oil) (11.42 g) in three portions (5 g, 4 g and 2.42 g) during a period of 30 minutes. The reaction mixture was stirred at 100°C for 2.5 hours. After cooling, water (200 ml) was added thereto and the mixture was concentrated. The residue was diluted by 1N hydrochloric acid at pH 1 and washed with ether. The aqueous layer was neutralized with 24% aqueous

sodium hydroxide to pH 7 and extracted with dichloromethane twice. The extract was washed with aqueous sodium chloride and dried over magnesium sulfate. Concentration of the resulting solution gave methyl 1-[2-(N,N-dimethylamino)methyl]indole-3-carboxylate (34.22 g) as an oil.

IR (Neat) : 3130, 3060, 2950, 2830, 2780, 1710-1690, 1618 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.17 (6H, s); 2.62 (2H, t, J=6.25Hz); 3.81 (3H, s); 4.33 (2H, t, d, d=6.25Hz); 7.15-7.30, 7.50-7.65, 7.95-8.05 (4H, m); 8.15 (1H, s)

Preparation 10

Methyl 1-[3-(N,N-dimethylamino)propyl]indole-3-carboxylate was prepared by reacting methyl indole-3-carboxylate with 3-(N,N-dimethylamino)propyl chloride in accordance with a similar manner to that of Preparation 9.

IR (Neat) : 1720-1690, 1620, 1540, 1470, 1400, 1385 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.8-2.0 (2H, m); 2.1-2.2 (8H, m); 3.81 (3H, s); 4.27 (2H, t, J=6.9Hz); 7.15-7.3 (2H, m); 7.55-7.6 (1H, m); 7.95-8.0 (1H, m); 8.13 (1H, s)

Preparation 11

Benzyl 1-[2-(tert-butoxycarbonylamino)ethyl]indole-3-carboxylate was prepared by reacting benzyl indole-3-carboxylate with 2-(tert-butoxycarbonylamino)ethyl methanesulfonate in accordance with a similar manner to that of Preparation 9.

mp : 104-107°C

IR (Nujol) : 3360, 1710, 1685 $cm^{-1}$

NMR ($CDCl_3$, δ) : 1.41 (9H, s); 3.49 (2H, dt, J=6.04,

5.94Hz); 4.20-4.40 (2H, m); 5.37 (2H, s); 7.10-7.50 (9H, m); 8.15-8.25 (1H, m); 7.82 (1H, s)

Preparation 12

A mixture of methyl 1-[2-(N,N-dimethylamino)-ethyl]indole-3-carboxylate (34.13 g) and 1N sodium hydroxide (277 ml) in methanol (340 ml) was heated under reflux for 4 hours. After cooling to room temperature, the mixture was acidified to pH 5 with 1N hydrochloric acid. This mixture was concentrated to 200 ml volume and the pH was adjusted to 5 again with 1N hydrochloric acid. The mixture was left standing under ice-cooling with seeding. The precipitates were collected by filtration to give 1-[2-(N,N-dimethylamino)ethyl]indole-3-carboxylic acid hydrochloride (20.46 g) as crystals.

IR (Nujol) : 2600, 2520, 2490, 1692, 1614, 1538 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 2.79 (6H, s); 3.50 (2H, t, J=7.22Hz); 4.74 (2H, t, J=7.20Hz); 7.15-7.40, 7.65-7.80, 7.95-8.10 (4H, m); 8.18 (1H, s); 11.18 (1H, br s); 12.12 (1H, br s)

Preparation 13

1-[3-(N,N-Dimethyl)propyl]indole-3-carboxylic acid was prepared by hydrolyzing the corresponding methyl ester compound in accordance with a similar manner to that of Preparation 12.

IR (Nujol) : 3400, 1690, 1585, 1575, 1530, 1410, 1310, 1225 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.8-2.05 (4H, m); 2.1-2.3 (6H, m); 4.27 (2H, t, J=6.8Hz); 5.45(1H, br s); 7.1-7.3 (2H, m); 7.5-7.6 (1H, m); 7.15-8.05 (2H, m)

Preparation 14

The benzyl-1-[2-(tert-butoxycarbonylamino)ethyl]-indole-3-carboxylate (3.70 g) was dissolved in a mixed solvent of ethanol (70 ml), tetrahydrofuran (20 ml) and acetic acid (5 ml). The solution was hydrogenated at atmospheric pressure with 10% palladium-carbon (0.50 g) for 5 hours. After removal of catalyst and evaporation of the solvent, ether was added to the crystalline residue. This product was washed with the same solvent, collected by filtration and dried to give 1-[2-(tert-butoxy-carboxylamino)ethyl]indole-3-carboxylic acid (2.43 g).

mp : 170-177°C

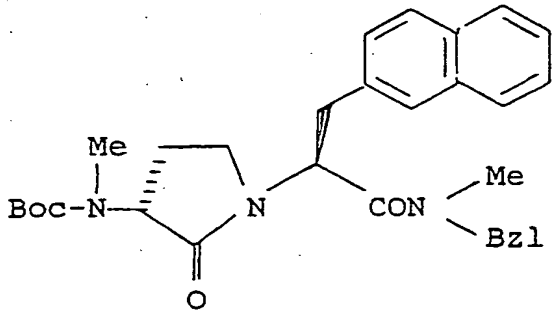
IR (Nujol) : 3430, 2545-2520, 1688, 1652, 1540 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.04, 1.31 (9H, s);
3.15-3.50 (2H, m); 4.10-4.45 (2H, m);
6.80-8.10 (6H, m); 11.88 (1H, br s)

Preparation 15

The product obtained in Preparation 1 was dissolved in methyl iodide (300 ml). The solution was stirred at room temperature for four hours. Then ether (60 ml) was added to the mixture and the resulting mixture was stirred for fifteen minutes and was left standing for three hours and forty-five minutes at room temperature. Methyl iodide (150 ml) and ether (240 ml) were added to the mixture and the mixture was left standing for additional fifteen hours at room temperature. Then the mixture was concentrated by rotary evaporator, and the residue was dissolved in a mixed solvent of tetrahydrofuran (300 ml) and dimethylformamide (100 ml). To the ice-cooled solution was added 60% sodium hydride (8.73 g) by portions in twenty minutes under nitrogen atmosphere. The reaction mixture was stirred for an hour at this temperature, then acetic acid (19.6 ml) was added into the mixture. After stirring the mixture for thirty minutes, water (100 ml)

was added into it under ice-cooling. After concentration, the residue was extracted with ethyl acetate. The organic layer was washed successively with water, aqueous sodium hydrogen carbonate solution, water, 0.5N hydrochloric acid and saturated sodium chloride solution, and dried over magnesium sulfate, and concentrated in vacuo. The crystalline residue was purified by recrystallization from 60% methanol (250 ml) to give the following compound (51.32 g).



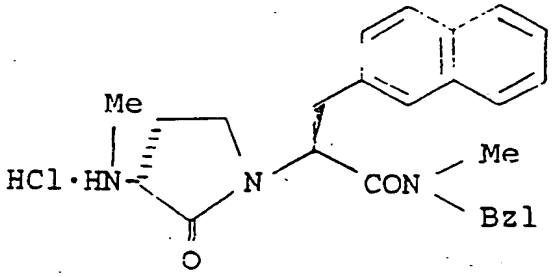

mp : 150-157°C

IR (Nujol) : 1692, 1640 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.29, 1.32 (9H, s); 1.69, 1.73, 1.84, 1.98 (3H, s); 1.50-2.30 (2H, m); 2.83, 2.87 (3H, s); 3.05-3.70 (4H, m); 3.95-4.80 (3H, m); 5.20-5.50 (1H, m); 6.95-7.95 (12H, m)

Preparation 16

The following compound was obtained by reacting the product prepared in Preparation 15 with 4N-hydrogen chloride in ethyl acetate in accordance with a similar manner to that of Preparation 7.

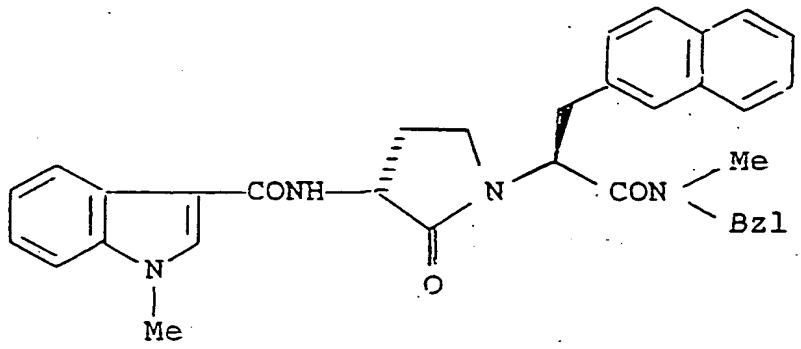



IR (Nujol) : 2650, 1679, 1643 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.15, 2.27 (3H, s); 1.80-2.45 (2H, m); 2.79, 2.83 (3H, s); 3.00-3.80 (4H, m); 4.05-4.75 (3H, m); 5.20-5.50 (1H, m); 6.80-8.00 (12H, m); 9.44 (2H, br s)

Example 1

To an ice-cooled suspension of 1-methylindole-3-carboxylic acid (190 mg), the product prepared in Preparation 7 (470 mg) and HOBT (150 mg) in dichloromethane (10 ml) was added WSCD (0.20 ml). The mixture was stirred at the same temperature for 35 minutes and at room temperature for 17 hours, during which period triethylamine in two portions (0.04 ml and 0.03 ml) were added to the mixture. To the solution was added N,N-dimethyl-1,3-propanediamine in three portions (0.022 ml, 0.03 ml and 0.05 ml) in 3 hours. After concentration, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous sodium hydrogencarbonate, water, 0.5N hydrochloric acid and saturated aqueous sodium chloride, and dried over magnesium sulfate. The solution was concentrated in vacuo, and diisopropyl ether was added to the residue. The precipitates were collected by filtration, washed with the same solvent and dried to give the following compound (0.34 g) as an amorphous solid.



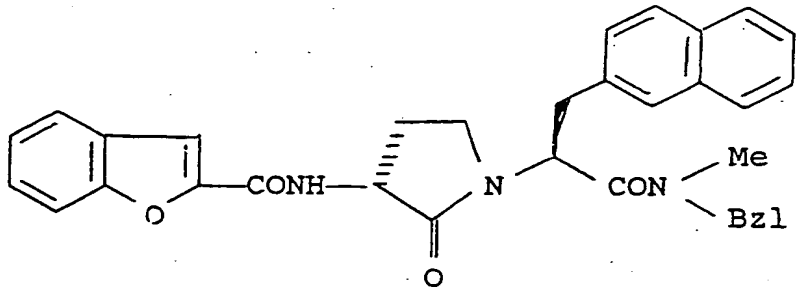

IR (Nujol) : 3330, 1693, 1640 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.80-2.00, 2.20-2.40 (2H, m); 2.758, 2.831 (3H, s); 2.90-3.75 (4H, m); 3.819, 3.831 (3H, s); 4.15-4.80 (3H, m); 5.20-5.50 (1H, m); 6.75-8.15 (18H, m)

Example 2

The following compounds were obtained in accordance with a similar manner to that of Example 1.

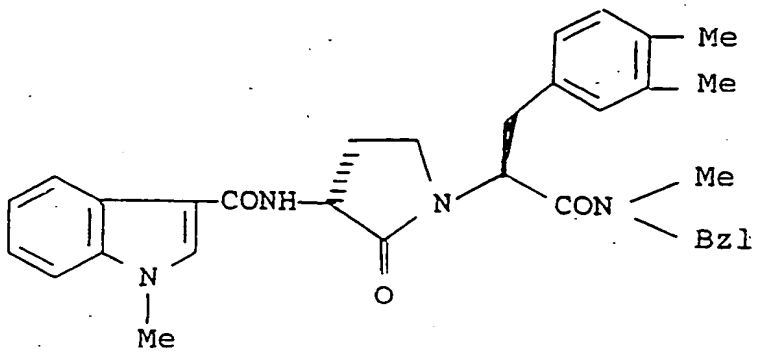
(1)




IR ($CHCl_3$) : 3300, 3003, 1690, 1655, 1640, 1596, 1562, 1510 $cm^{1}$

NMR (DMSO-$d_6$, $\delta$) : 2.00-2.50 (2H, m); 2.757, 2.815 (3H, s); 2.90-3.80 (4H, m); 4.10-4.80 (3H, m); 5.251, 5.421 (1H, dd); 6.70-8.00 (18H, m)

(2)

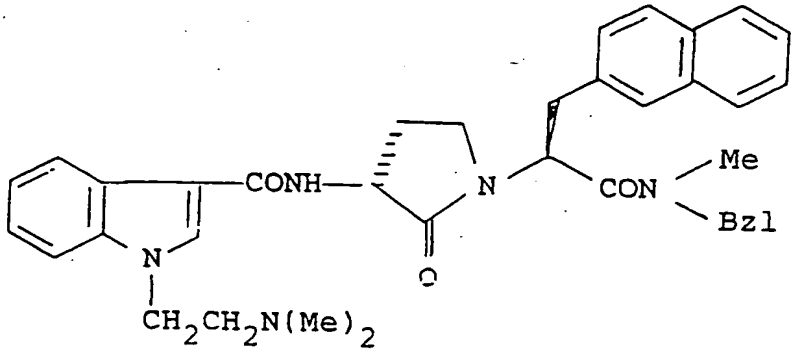



IR (Nujol) : 3280, 1640, 1538 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.75-2.25 (2H, m); 2.14, 2.20 (6H, s); 2.25-2.90 (2H, m); 2.76, 2.82 (3H, s); 3.20-3.65 (2H, m); 3.82, 3.83 (3H, s); 4.20-4.80 (3H, m); 5.05-5.30 (1H, m); 6.80-7.30, 7.40-7.55, 7.90-8.20 (14H, m)

MASS ($M^+$) : 536

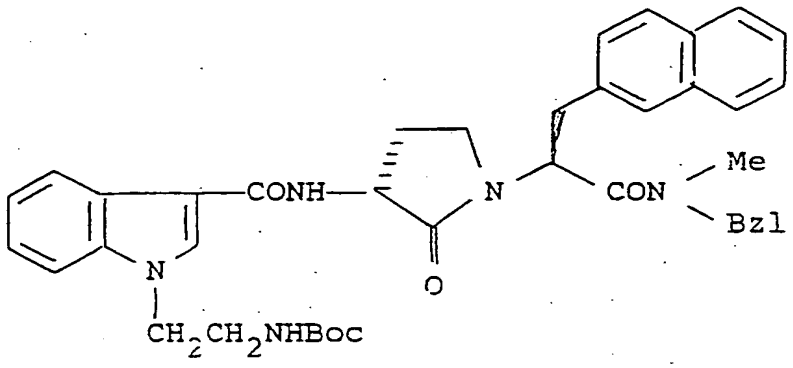
(3)




NMR (DMSO-$d_6$, $\delta$) : 1.80-2.45 (2H, m); 2.18, 2.19 (6H, s); 2.55-2.65 (2H, m); 2.76-2.83 (3H, s); 2.90-3.75 (4H, m); 4.15-4.80 (5H, m); 5.20-5.50 (1H, m); 6.70-8.20 (18H, m)

MASS ($M^+$) : 615

(4)

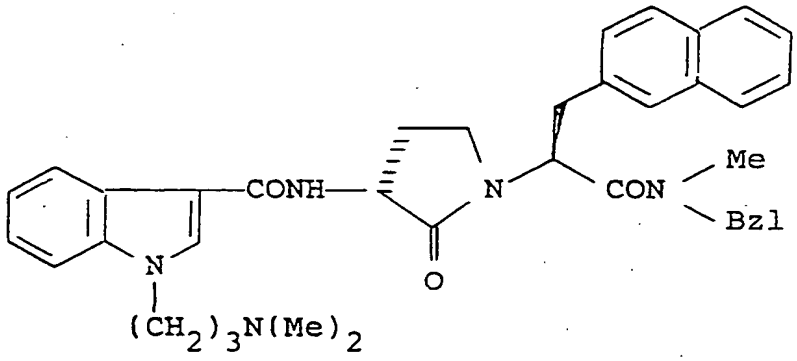



IR (Nujol) : 3330, 1695, 1645, 1539 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.14, 1.33 (9H, s); 1.70-2.45 (2H, m); 2.76, 2.81, 2.83 (3H, s); 2.90-3.80 (6H, m); 4.10-4.80 (5H, m); 5.15-5.50 (1H, m); 6.70-8.20 (19H, m)

MASS ($M^+$) : 687

(5)



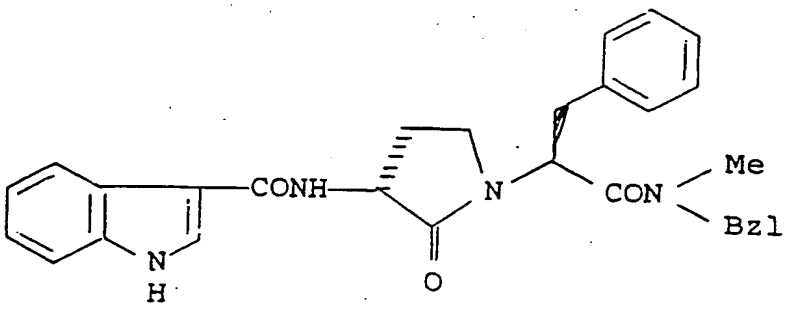

IR ($CHCl_3$) : 3330, 1695, 1645, 1545, 1470-1450, 1280 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.8-2.0 (5H, m); 2.1-2.5 (7H, m); 2.76, 2.83 (3H, s); 2.8-3.15 (2H, m); 3.25-3.75 (2H, m); 4.15-4.8 (5H, m); 5.2-5.5 (1H, m); 6.75-8.15 (18H, m)

MASS ($M^+$) : 629

Example 3

To a solution of the product prepared in Preparation 8-(1) (0.63 g) and bis(trimethylsilyl)acetamide (0.99 g) in dichloromethane (20 ml) was added indole-3-carbonyl chloride (0.35 g) under ice-cooling, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated, and the concentrate was dissolved in tetrahydrofuran (20 ml). To this solution was added 1N hydrochloric acid (2 ml) under ice-cooling, and the mixture was stirred for 30 minutes. The reaction mixture was concentrated and the concentrate was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogencarbonate and aqueous sodium chloride, and then dried over magnesium sulfate. The solution was evaporated in vacuo, and the residue (0.8 g) was chromatographed on silica gel (30 g). Elution was carried out with chloroform and then a mixture of chloroform and methanol (99:1 to 98:2). The fractions containing the desired compound were combined and evaporated in vacuo, and the residue (560 mg) was triturated with a mixture of ethyl acetate and diisopropyl ether to give the following compound (440 mg).




IR (Nujol) : 3250, 1674, 1623, 1582, 1554, 1492 $cm^{-1}$

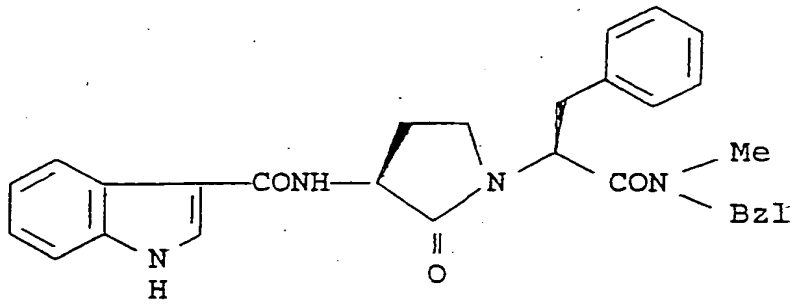
NMR (DMSOd-$_6$, $\delta$) : 1.8-2.0, 2.2-2.5 (2H, m); 2.758, 2.806 (3H, s); 2.7-3.0 (2H, m); 3.3-3.7 (2H, m); 4.2-4.6 (1H, m); 4.6-4.8 (2H, m); 5.1-5.4 (1H, m); 6.8-7.3 (2H, m)(10H, m); 7.4-7.5 (1H, s);

8.0-8.2 (2H, m)(1H, s); 11.5776 (1H, s)

Example 4

The following compounds were obtained by reacting the corresponding starting compounds with indole-3-carbonyl chloride or cinnamoyl chloride in accordance with a similar manner to that of Example 3.

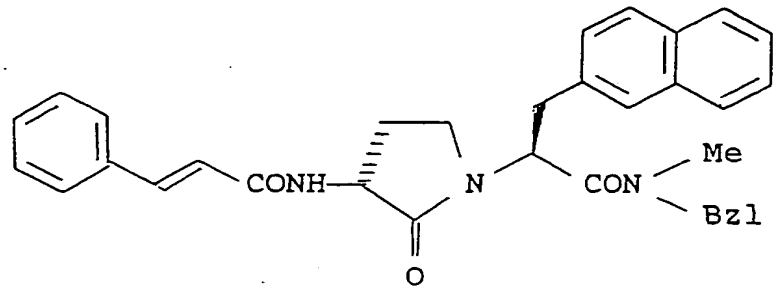
(1)




IR (Nujol) : 3220, 1685, 1640, 1630, 1535 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.85-2.1 (1H, m); 2.3-2.4 (1H, m); 2.81, 2.93 (3H, s); 2.9-3.2 (2H, m); 3.4-3.6 (2H, m); 4.4 (1H, m); 4.43, 4.63 (ABq, J=14.9Hz); 4.35, 4.93 (J=16.9Hz); 5.19, 5.32 (1H, t); 6.95-7.5 (13H, m); 8.0-8.2 (3H, m); 11.57 (1H, s)

(2)

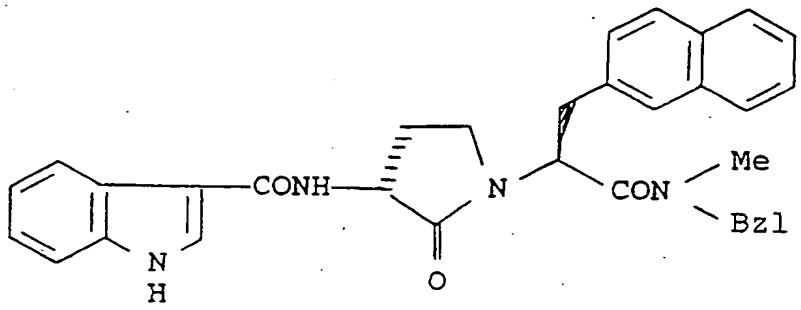



IR ($CHCl_3$) : 3300, 3175, 1692, 1655, 1546 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.60-2.40 (2H, m); 2.831, 2.767

(3H, s); 2.95-3.70 (4H, m); 4.15-4.80 (3H, m); 5.262, 5.417 (1H, d,d, J=7.0Hz, 8.2Hz); 6.50-8.00 (20H, m)

(3)

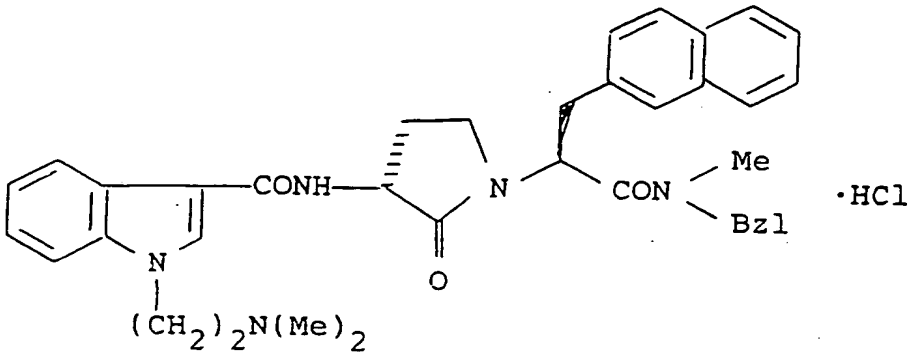



IR (Nujol) : 3200, 1615, 1525 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.75-2.45 (2H, m); 2.76, 2.83 (3H, s); 2.90-3.75 (4H, m); 4.15-4.80 (3H, m); 5.20-5.50 (1H, m); 6.75-8.20 (18H, m); 11.57 (1H, s)

Example 5

To an ice-cooled solution of the product obtained in Example 2-(3) (0.32 g) in ethyl acetate (10 ml) was added 4N-hydrogen chloride in ethyl acetate (0.19 ml). The reaction mixture was stirred for 5 minutes. After evaporation of the solvent, ether was added to the residue and the resulting precipitate were collected by filtration and dried to give the following compound (0.34 g) as an amorphous solid.

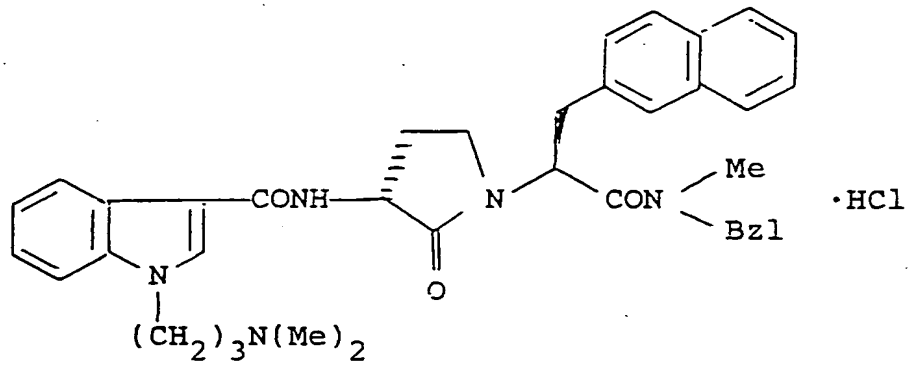


IR (Nujol) : 3300-3450, 1644, 1547 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.80-2.55 (2H, m); 2.76, 2.83 (9H, s); 2.90-3.80 (6H, m); 4.15-4.80 (5H, m); 5.20-5.50 (1H, m); 6.70-8.30 (18H, m); 10.85 (1H, br s)

Example 6

The following compound was obtained in accordance with a similar manner to that of Example 5.



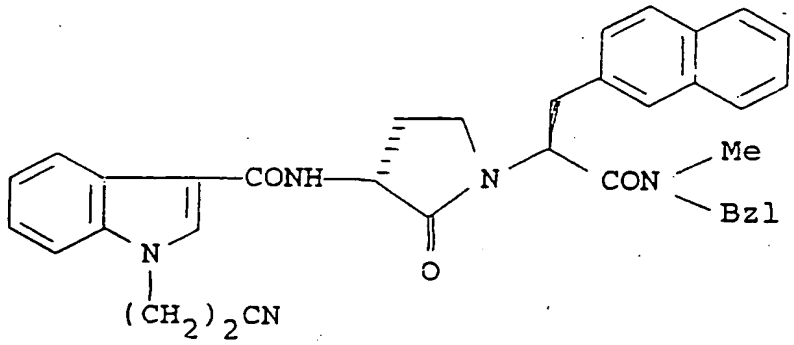

IR ($CHCl_3$) : 1695, 1645, 1545, 1465, 1400, 1280 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.85-2.05 (1H, m); 2.1-2.45 (3H, m); 2.6-2.8 (6H, m); 2.83 (3H, s); 2.95-3.2 (4H, m); 3.3-3.75 (2H, m); 4.15-4.75 (5H, m); 5.2-5.5 (1H, m); 6.95-8.2 (18H, m); 10.65 (1H, br s);

Example 7

To an ice-cooled solution of the product obtained in Example 4-(3) (1.19 g), and acrylonitrile (0.58 g) in dioxane (25 ml) was added dropwise Triton B (40% in methanol) (0.11 ml). The solution was stirred at the same temperature for 20 minutes and at room temperature for further 2 hours. To the mixture was added chloroform to dissolve precipitates. Water was added to this solution, and the organic layer was separated. The aqueous layer was extracted twice with chloroform. The combined organic layer was dried over magnesium sulfate and concentrated in

vacuo. The concentrate was subjected to column chromatography on silica gel (40 g) eluting with a mixed solvent of chloroform and methanol (from 0% to 5% gradient elution). The residue after removal of the solvent was further purified by a medium-pressure silica gel column chromatography eluting successively with a mixed solvent of ethyl acetate and toluene (2:1 and 4:1) ethyl acetate alone and a mixed solvent of ethyl acetate and methanol (5%). The fractions containing the desired compound were concentrated to give the following compound (0.56 g) as an amorphous solid.




IR ($CHCl_3$) : 3440, 3000, 1695, 1650, 1547 $cm^{-1}$

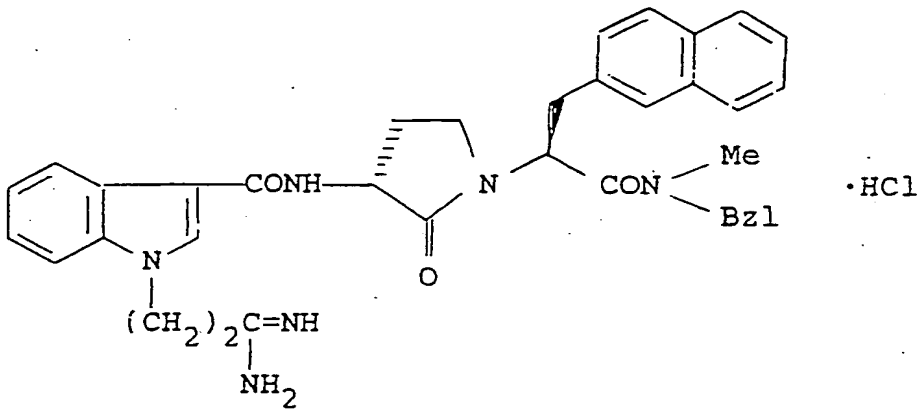
NMR (DMSO-$d_6$, $\delta$) : 1.80-2.10, 2.25-2.45 (2H, m); 2.76, 2.83 (3H, s); 3.00-3.15 (2H, m); 2.90-3.75 (4H, m); 4.15-4.80 (5H, m); 5.20-5.50 (1H, m); 6.70-8.25 (18H, m)

FAB-MASS $(M+1)^+$ : 598.3

Example 8

To an ice-cooled solution of saturated hydrogen chloride in ethanol (25 ml) was added the product obtained in Example 7 (0.45 g). The solution was stirred at the same temperature for 1.5 hours. After concentration, the residue was dissolved in anhydrous ethanol (10 ml). To the solution was added a solution of 4N ammonia in ethanol (47 ml) under ice-cooling. The mixture was stirred at

room temperature for 2.5 hours. After concentration, ether was added to the residue, and the resulting precipitates were collected by filtration and dried to give the following compound (0.30 g) as an amorphous solid.

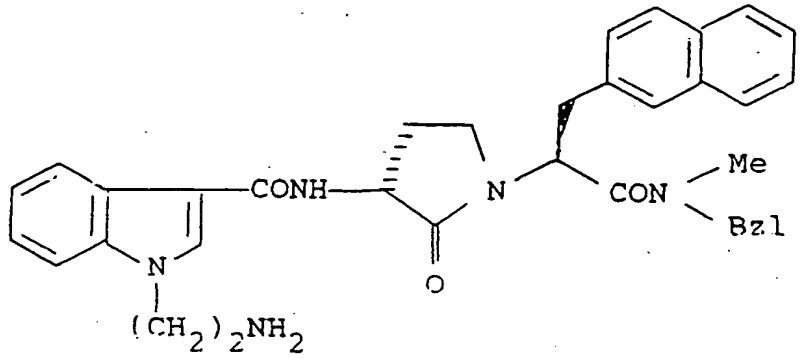



IR (Nujol) : 3260, 1700-1660, 1545 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.85-2.05, 2.25-2.45 (2H, m); 2.76, 2.83 (3H, s); 2.90-3.05 (2H, m); 3.05-3.80 (4H, m); 4.15-4.80 (5H, m); 5.20-5.50 (1H, m); 6.75-8.30 (18H, m); 8.69, 9.25 (4H, br s)

Example 9

To an ice-cooled solution of the product obtained in Example 2-(4) (3.96 g) in ethyl acetate (40 ml) were added successively anisole (4.0 ml) and 4N hydrogen chloride in ethyl acetate (40 ml). The solution was stirred at the same temperature for 15 minutes and at the room temperature for 2 hours. After concentration, ether was added to the residue, and the resulting precipitates were collected by filtration and dried to give the following compound (3.04g) as an amorphous solid.

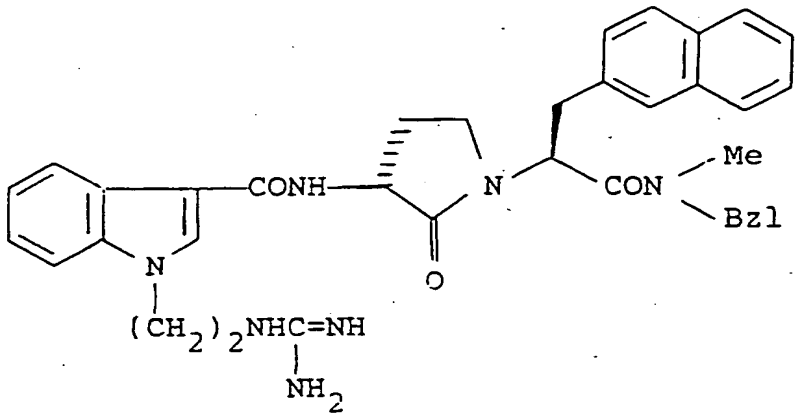



IR (Nujol) : 3500-3100 (br), 1630, 1530 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.80-2.25 (2H, m); 2.76, 2.81, 2.83 (3H, s); 2.90-3.80 (6H, m); 4.10-4.80 (5H, m); 5.20-5.50 (1H, m); 6.75-8.40 (21H, m)

Example 10

To a solution of the product obtained in Example 9 (0.50 g) and 3,5-dimethylpyrazole-1-carboxamidine nitrate (0.16 g) in dimethylformamide (15 ml) was added triethylamine (0.22 ml) at room temperature, and the solution was stirred for 7 hours at the same temperature. After 3,5-dimethylpyrazole-1-carboxamidine nitrate (0.32 g) and triethylamine (0.44 ml) were added to the solution, the mixture was stirred for 5 days at the same temperature. After concentration, water was added to the residue and the pH was adjusted to 4 with 1N hydrochloric acid. After the aqueous solution was extracted with ethyl acetate, the extract was concentrated in vacuo. The residue was purified on a column of alumina (20 g) eluting successively with a mixed solvent of chloroform and methanol (10:1, 4:1 and then 1:1). Ether was added to the residue, and the resulting precipitates were collected by filtration and dried to give the following compound (0.32 g) as an amorphous solid.



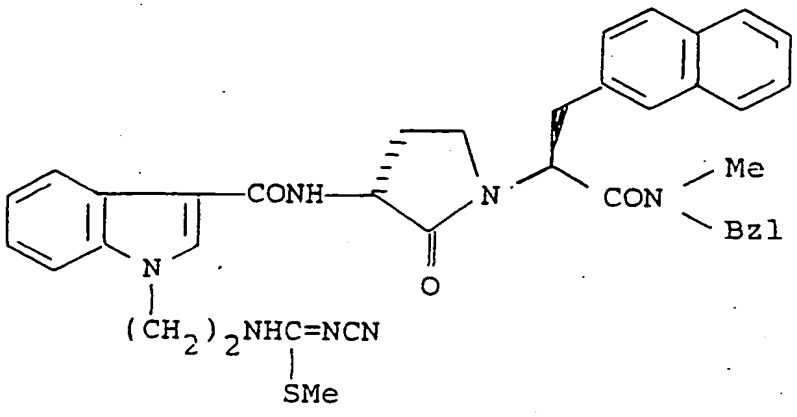

IR (Nujol) : 3300, 3150, 1620, 1530 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.80-2.45 (2H, m); 2.76, 2.83 (3H, s); 2.90-3.75 (6H, m); 4.15-4.80 (5H, m); 5.20-5.50 (1H, m); 6.75-8.20 (22H, m)

FAB-MASS $(M+1)^+$ : 630.3

Example 11

To an ice-cooled solution of the product obtained in Example 9 (624 mg) in ethanol (6 ml) was added triethylamine (0.14 ml). After stirring for 20 minutes, the resulting solution was added to a solution of carbonimidodithioic acid cyanodimethyl ester [$(MeS)_2C=N-CN$] (324 mg) in ethanol (6 ml) at room temperature. The solution was stirred for a day at the same temperature. After concentration, the residue was extracted with ethyl acetate. The extract was washed successively with 0.5N hydrochloric acid and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20 g) eluting with a mixed solvent of chloroform-methanol (from 0% to 2% gradient elution) to give the following compound (0.58 g) as an amorphous solid.



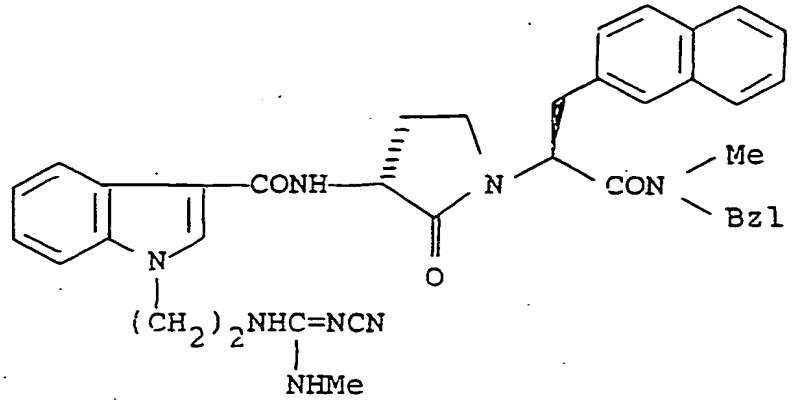

IR ($CHCl_3$) : 3300, 3000, 2180, 1622, 1535 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.85-2.45 (2H, m); 2.38, 2.39 (3H, s); 2.76, 2.83 (3H, s); 2.90-3.75 (6H, m); 4.15-4.80 (5H, m); 5.20-5.50 (1H, m); 6.75-8.50 (19H, m)

FAB-MASS $(M + 1)^+$ : 686.3

Example 12

To a solution of the product obtained in Example 11 (0.55 g) in methanol (5 ml) was added a solution of 40% methylamine in methanol (10 ml) at room temperature. The solution was stirred for 21 hours at the same temperature. After concentration, the residue was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20 g) eluting with a mixed solvent of chloroform and methanol (from 0% to 1.5% gradient elution). The solvent was removed from the fractions and diisopropyl ether was added to the residue. The resulting precipitates were collected by filtration, washed with the same solvent and dried to give the following compound (0.34 g) as an amorphous solid.



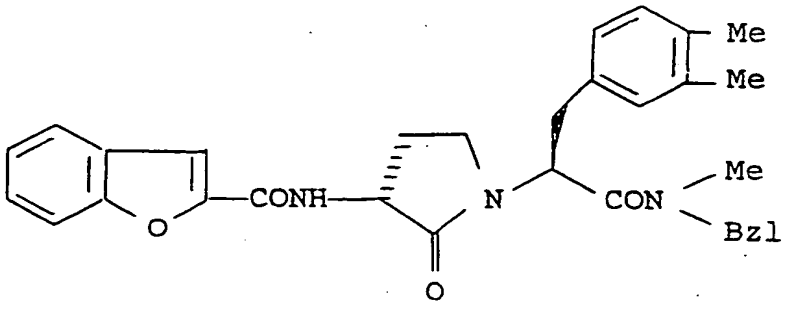
IR (Nujol) : 3300, 2180, 1680, 1640, 1580, 1540 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.75-2.45 (2H, m); 2.58, 2.60 (3H, s); 2.76, 2.83 (3H, s); 2.90-3.75 (6H, m); 4.10-4.80 (5H, m); 5.20-5.50 (1H, m); 6.70-8.35 (20H, m)

FAB-MASS $(M + 1)^+$ : 669.2

Example 13

The following compound was obtained by reacting the corresponding starting compound with benzofuran-2-carboxylic acid in accordance with a similar manner to that of Example 1.



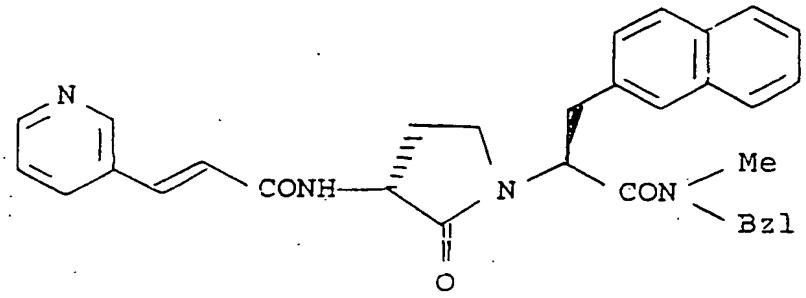
IR (Nujol) : 3250, 1645, 1595 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.75-2.95 (4H, m); 2.14, 2.20 (6H, s); 2.76, 2.81 (3H, s); 3.15-3.70 (2H, m); 4.15-4.80 (3H, m); 5.00-5.30 (1H, m); 6.70-7.85, 8.85-9.10 (14H, m)

Example 14

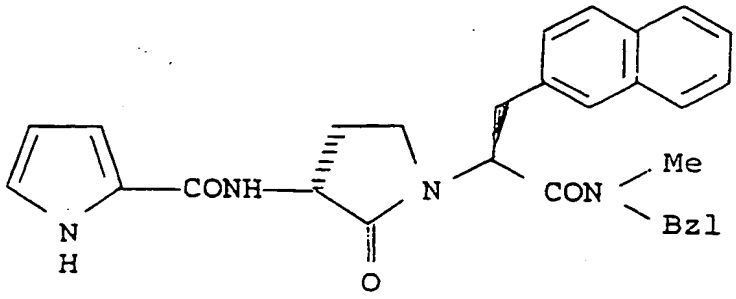
The following compounds were obtained in accordance with a similar manner to that of Example 1.

(1)




NMR (DMSO-$d_6$, δ) : 1.60-1.95, 2.25-2.50 (2H, m); 2.77, 2.83 (3H, s); 2.90-3.75 (4H, m); 4.15-4.80 (3H, m); 5.20-5.50 (1H, m); 6.65-8.80 (19H, m)

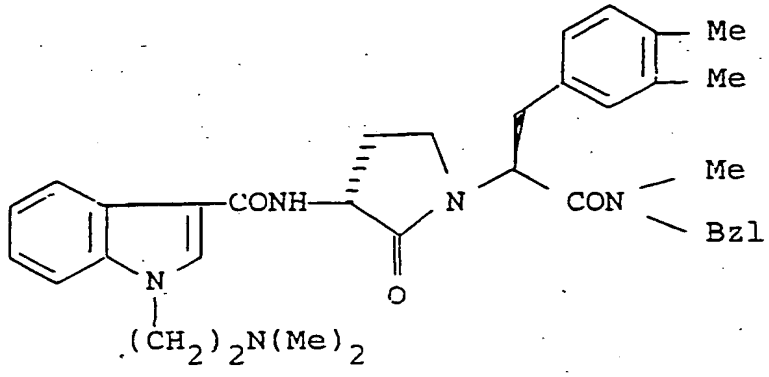
(2)




IR (Nujol) : 3300, 1685, 1640, 1562, 1525 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.75-2.45 (2H, m); 2.74, 2.81 (3H, s); 2.85-3.75 (4H, m); 4.10-4.80 (3H, m); 5.20-5.50 (1H, m); 6.09 (1H, m); 6.65-8.35 (15H, m); 11.49 (1H, s)

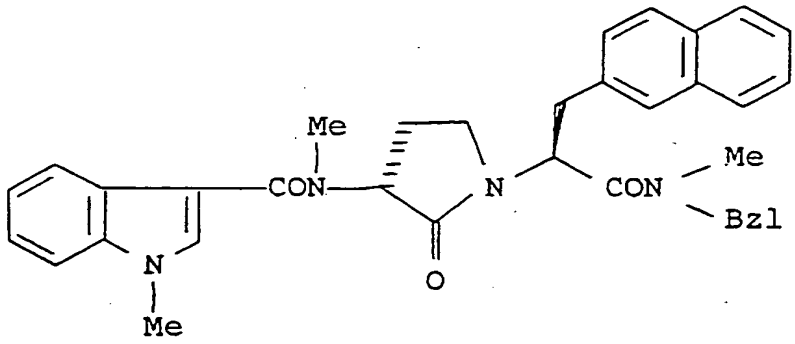
(3)




IR ($CHCl_3$) : 3320, 2940, 1645, 1540, 755, 700 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.80-2.45 (2H, m); 2.18, 2.19 (12H, s), 2.55-2.65 (2H, m); 2.76, 2.82 (3H, s); 2.65-2.90, 3.20-3.40 (2H, m); 3.20-3.70 (2H, m); 4.20-4.80 (5H, m); 5.05-5.35 (1H, m); 6.80-7.30, 7.50-7.60, 8.00-8.20 (14H, m)

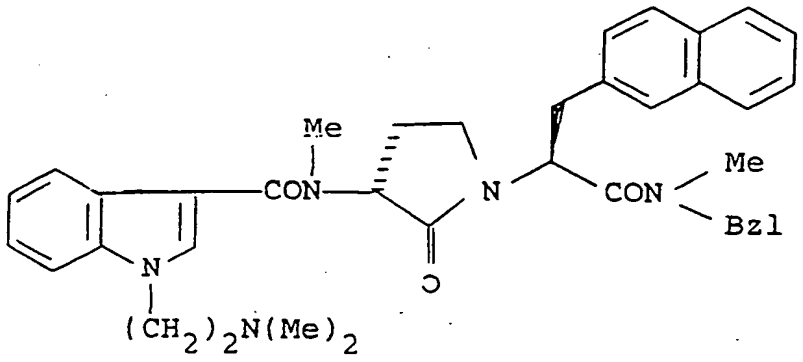
(4)




IR (Nujol) : 1690, 1640, 1530, 740 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.65-2.40 (5H, m); 2.84, 2.88 (3H, s), 3.10-3.40, 3.55-3.75 (4H, m); 3.78, 3.80 (3H, s); 4.25-4.75, 5.00-5.20 (3H, m); 5.35-5.55 (1H, m); 6.90-7.90 (17H, m)

(5)

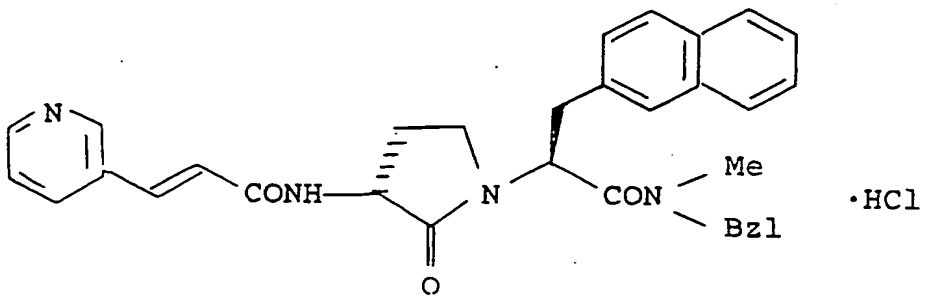


NMR (DMSO-$d_6$, δ) : 1.70-2.20 (2H, m); 2.12, 2.15 (9H, s); 2.50-2.65 (2H, m); 2.84, 2.88 (3H, s); 3.10-3.40 (4H, m); 3.60-3.75 (1H, m); 4.15-4.35 (2H, m); 4.35-4.70 (2H, m); 5.00-5.55 (1H, m); 6.90-7.90 (17H, m)

Example 15

The following compounds were obtained in accordance with a similar manner to that of Example 5.

(1)

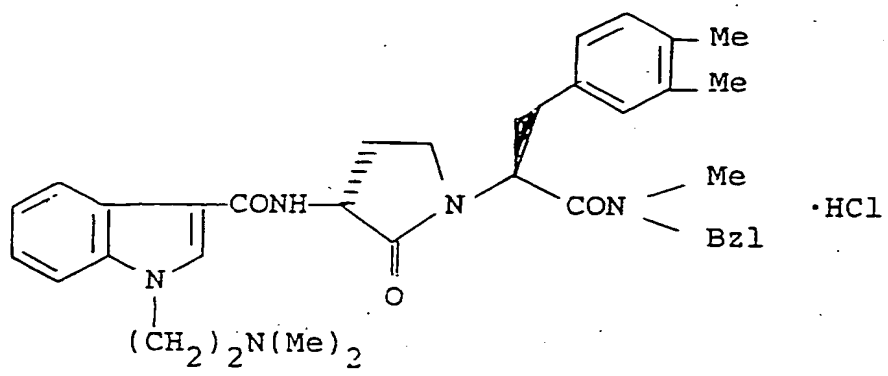


IR (Nujol) : 3430-3200, 1640, 1547, 810 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.65-1.95, 2.25-2.50 (2H, m); 2.77, 2.83 (3H, s); 2.90-3.75 (4H, m); 4.15-4.80

(3H, m); 5.15-5.45 (1H, m); 5.00-6.00 (1H, br s); 6.75-9.05 (19H, m)

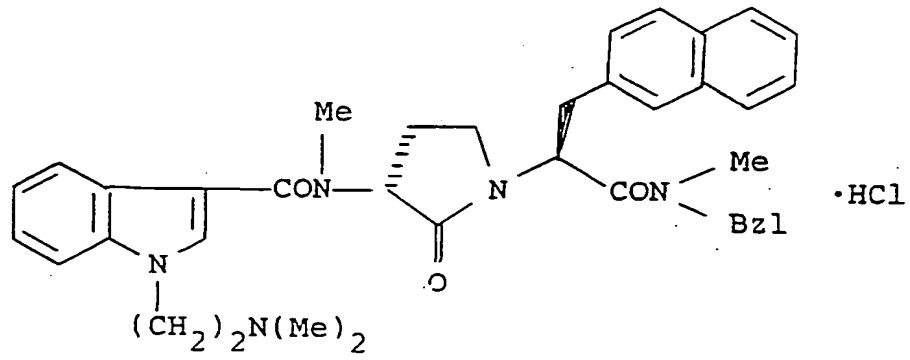
(2)




IR (Nujol) : 3400, 1640, 1540, 750 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.80-2.40 (2H, m); 2.14, 2.20 (6H, s); 2.76, 2.82 (9H, s); 2.70-2.95, 3.20-3.65 (6H, m); 4.20-4.80 (5H, m); 5.00-5.30 (1H, m); 6.80-7.40, 7.80-7.75, 8.10-8.30 (14H, m); 10.92 (1H, br s)

(3)



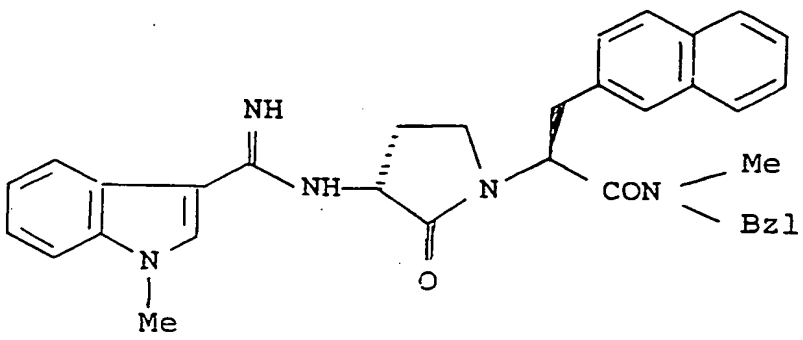

IR (Nujol) : 3400, 1692, 1643-1612, 1535, 740 $cm^{-1}$

NMR (DMSO-$d_6$ + $D_2O$, δ) : 1.65-2.40 (5H, m); 2.80, 2.81 (6H, s); 2.84-2.88 (3H, s); 3.10-3.80 (7H,

m); 4.25-4.75 (4H, m); 5.00-5.55 (1H, m); 6.90-7.90 (17H, m).

Example 16

To the product prepared in Example 1 in methylene chloride (40 ml) was added a solution of N,N-dimethyl-aniline (242 mg) dissolved in methylene chloride (10 ml) at -30°C under nitrogen atmosphere and the solution was stirred at the same temperature for fifteen minutes. Then phosphorus pentachloride (416 mg) was added to the reaction mixture keeping the temperature between -40°C and -30°C, and the solution was stirred for one and half hours at -40°C. A solution of ammonia dissolved in ethanol (10 ml) was added dropwise and the solution was stirred for an hour at the same temperature. The temperature of the solution was risen up to room temperature, and a saturated potassium carbonate solution was added and the mixture was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on alumina (25 g) eluting with chloroform and further eluting with a mixed solvent of chloroform-methanol (10:1) to give the following compound (0.33 g) as an amorphous solid.

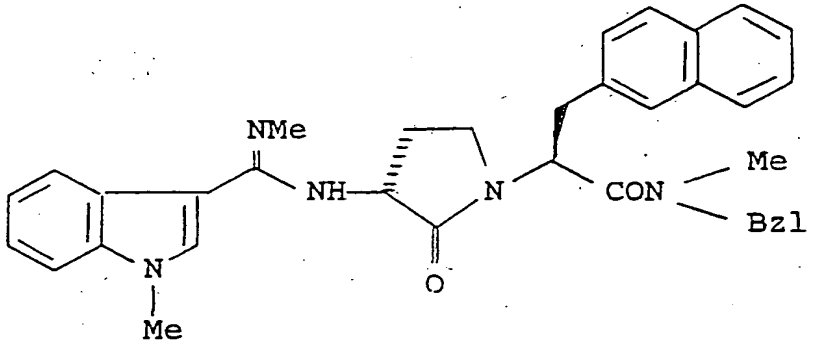



IR ($CHCl_3$) : 3370, 3060, 3020, 2940, 1640, 1600, 1543 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.75-2.00, 2.25-2.50 (2H, m); 2.79, 2.85 (3H, s); 2.90-3.85 (4H, m); 3.78, 3.79 (3H, s); 4.00-4.85 (3H, m); 5.20-5.45 (1H, m); 6.09 (1H, br s); 6.80-8.35 (18H, m)

Example 17

The following compound was obtained in accordance with a similar manner to that of Example 16.



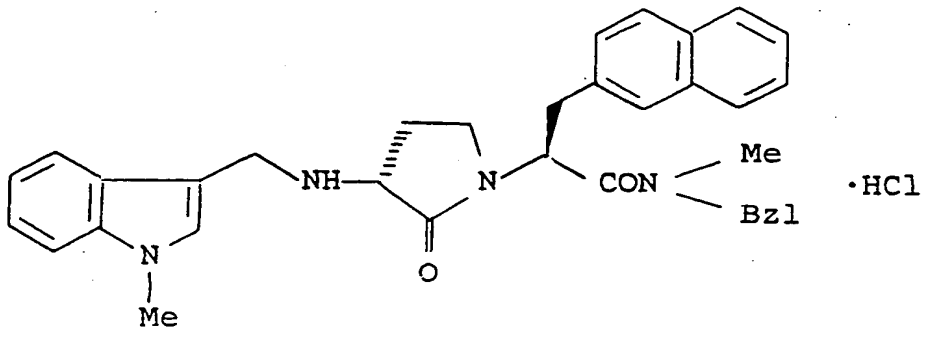

IR ($CHCl_3$) : 3400, 2950, 1680, 1642, 1540 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.70-2.20 (2H, m); 2.61, 2.65 (3H, s); 2.70, 2.79 (3H, s); 2.90-3.70 (4H, m); 3.76 (3H, s); 3.80-4.75 (3H, m); 5.15-5.40 (1H, m); 6.11 (1H, br s); 6.70-7.95 (17H, m)

Example 18

The product prepared in Preparation 7 was distributed between chloroform and aqueous sodium hydrogen carbonate solution and the organic layer was separated and was dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in a mixed solvent of 1,4-dioxane (2 ml) and ethyl acetate (2 ml). To the solution was added formalin solution (37%) (0.09 ml) under ice-cooling, and the solution was stirred for one and half hours at this temperature. Then 1-methylindole (150 mg) dissolved in 1,4-dioxane (2 ml) was added into the mixture at this

temperature. The mixture was stirred for fifteen minutes under ice-cooling and for four hours at room temperature, during which period formalin solution (37%) (0.09 ml) was added. The solution was left standing overnight in a refrigerator and was stirred for additional seven and half hours at room temperature. Water was added to the mixture and the acidity of the mixture was adjusted to pH 8 with aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (30 g) eluting with mixed solvent of. chloroform-methanol (from 0% to 1% gradient elution). The product (180 mg) was dissolved in tetrahydrofuran (7.5 ml) and 4N-hydrogen chloride in dioxane (0.12 ml) was added under ice-cooling. The solution was stirred for forty minutes at room temperature. After concentration, diisopropyl ether was added to the residue and the resulting precipitates were filtered, and dried to give the following compound (0.14 g) as amorphous solid.

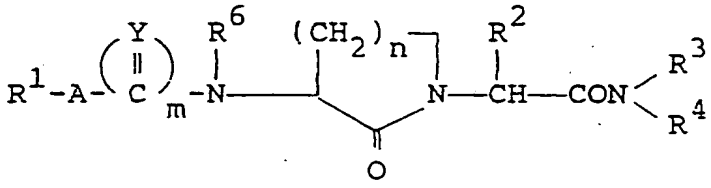



IR (Nujol) : 3450, 1697, 1646 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 2.00-2.55 (2H, m), 2.782, 2.844 (3H, s), 2.80-3.90 (6H, m), 3.792 (3H, s), 4.00-4.80 (3H, m), 5.25-5.55 (1H, m), 6.75-7.95 (17H, m), 9.40-9.70 (1H, br s)

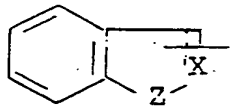
CLAIMS

1. A compound of the formula:



(I)

wherein $R^1$ is aryl, pyridyl, pyrrolyl, or a group of the formula :



wherein the line and the dotted line are a single bond or a double bond,
X is CH or N and
Z is -O-, -S- or -NH-,
each of which may have suitable substituent(s);

$R^2$ is ar(lower)alkyl which may have suitable substituent(s);

$R^3$ is lower alkyl which may have suitable substituent(s);

$R^4$ is ar(lower)alkyl which may have suitable substituent(s);

$R^6$ is hydrogen or lower alkyl;

A is bond, lower alkylene or lower alkenylene;

Y is O or N-$R^7$ in which $R^7$ is hydrogen or lower alkyl;

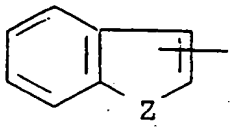
m is 0 or 1; and

n is an integer of 0 to 2,

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

$R^1$ is $C_6$-$C_{10}$ aryl, pyridyl, pyrrolyl, or a group of the formula :




,

in which Z is $-N-$ or $-O-$, wherein
$|$
$R^5$

$R^5$ is hydrogen;
lower alkyl;
di(lower)alkylamino(lower)alkyl;
amino(lower)alkyl;
acylamino(lower)alkyl;
cyano(lower)alkyl;
amidino(lower)alkyl;
guanidino(lower)alkyl;
[2-lower alkyl-3-cyanoisothioureido]-(lower)alkyl; or
[3-lower alkyl-2-cyanoguanidino]-(lower)alkyl;

$R^2$ is $C_6$-$C_{10}$ ar(lower)alkyl;

$R^3$ is lower alkyl;

$R^4$ is $C_6$-$C_{10}$ ar(lower)alkyl;

$R^6$ is hydrogen or lower alkyl;

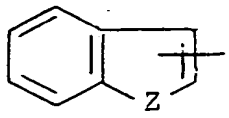
A is bond or lower alkenylene;

Y is O or N-$R^7$ in which $R^7$ is hydrogen or lower alkyl;

m is 0 to 1; and

n is an integer of 1.

3. A compound of claim 2, wherein
$R^1$ is phenyl, pyridyl, pyrrolyl, or a group of the formula :



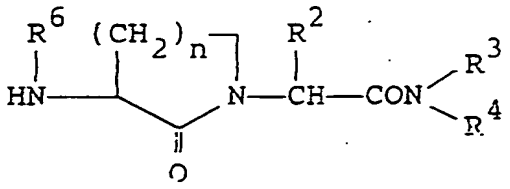
in which Z is -N- or -O-, wherein
$R^5$

$R^5$ is hydrogen;
lower alkyl;
di(lower)alkylamino(lower)alkyl;
amino(lower)alkyl;
lower alkoxycarbonylamino(lower)alkyl;
cyano(lower)alkyl;
amidino(lower)alkyl;
guanidino(lower)alkyl;
[2-lower alkyl-3-cyanoisothioureido]-(lower)alkyl; or
[3-lower alkyl-2-cyanoguanidino]-(lower)alkyl;

$R^2$ is phenyl(lower)alkyl, mono or di(lower)alkyl-phenyl(lower)alkyl, naphthyl(lower)alkyl; and
$R^4$ is phenyl(lower)alkyl.

4. A process for preparing a compound (I), or a salt thereof which comprises

(1) reacting a compound of the formula:

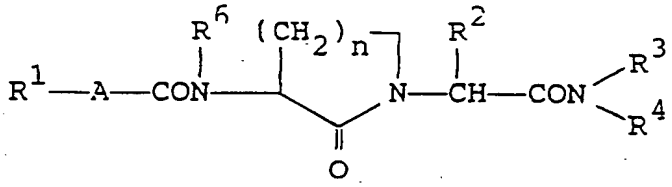


(II)

wherein $R^2$, $R^3$, $R^4$, $R^6$ and n are each as defined above,
or its reactive derivative at the amino group,
or a salt thereof, with a compound of the formula:

$$R^1\text{-A-COOH} \qquad \text{(III)}$$

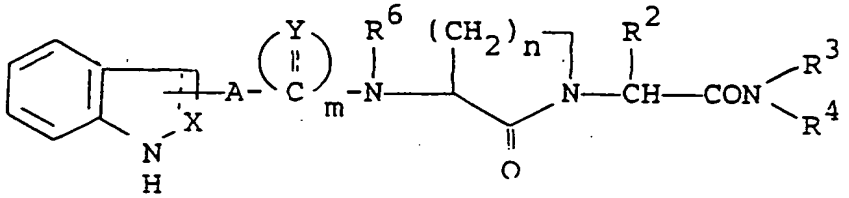
wherein $R^1$ and A are each as defined above,
or its reactive derivative at the carboxy group,
or a salt thereof, to give a compound of the formula :



(I-a)

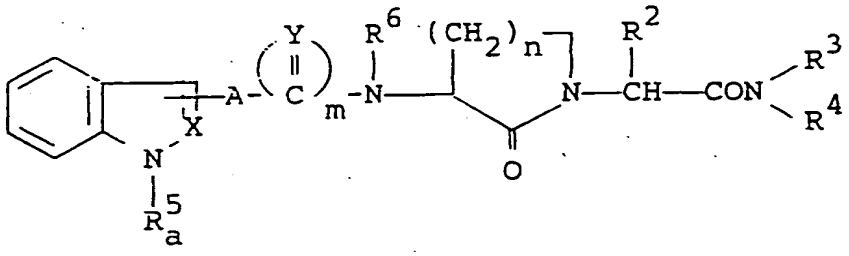
wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, A and n are each as defined above,
or a salt thereof, or

(2) subjecting a compound of the formula :



(I-b)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above,
or a salt thereof, to addition reaction of cyano-(lower)alkene, to give a compound of the formula :



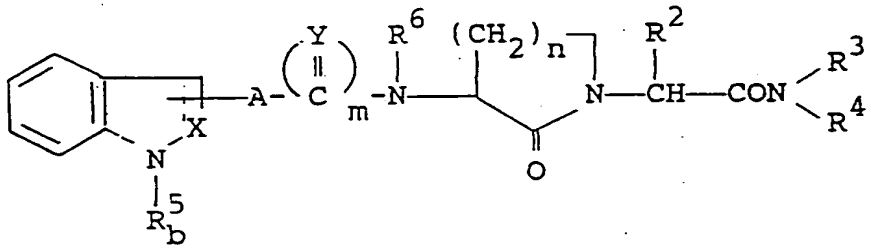
(I-c)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above, and

$R^5_a$ is cyano(lower)alkyl,

or a salt thereof, or

(3) reacting the compound (I-c) or a slat thereof with ammonia or a salt thereof to give a compound of the formula :



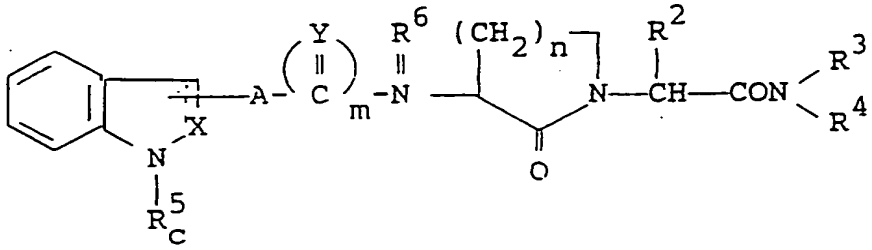
(I-d)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above, and

$R^5_b$ is amidino(lower)alkyl,

or a salt thereof, or

(4) subjecting a compound of the formula :



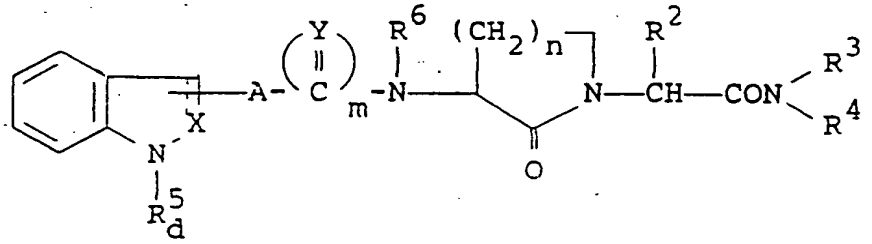
(I-e)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each

as defined above, and

$R^5_c$ is protected amino(lower)alkyl,

or a salt thereof, to removal reaction of the amino-protective group in $R^5_c$, to give a compound of the formula :



(I-f)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above, and

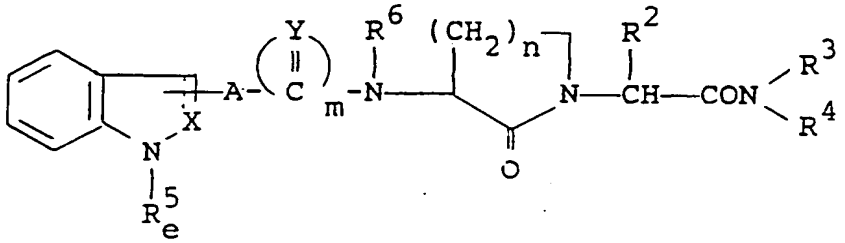
$R^5_d$ is amino(lower)alkyl,

or a salt thereof, or

(5) reacting the compound (I-f) or a salt thereof with a compound of the formula :

$$L\text{-}R^a \qquad (IV)$$

wherein $R^a$ is amidino or (lower)alkylthio)-(cyanoimino)methyl, and L is a leaving group, to give a compound of the formula :



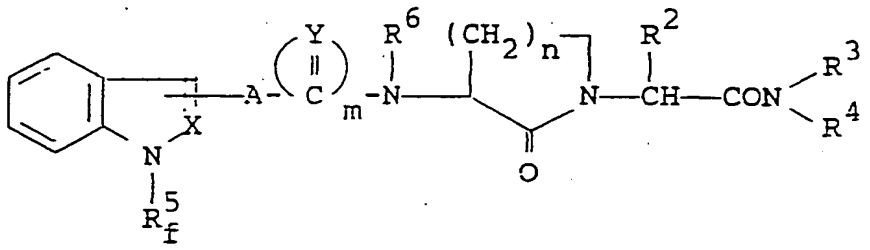
(I-g)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above, and

$R^5_e$ is guanidino(lower)alkyl or [2-lower alkyl-3-cyanoisothioureido](lower)alkyl,

or a salt thereof, or

(6) reacting a compound of the formula :



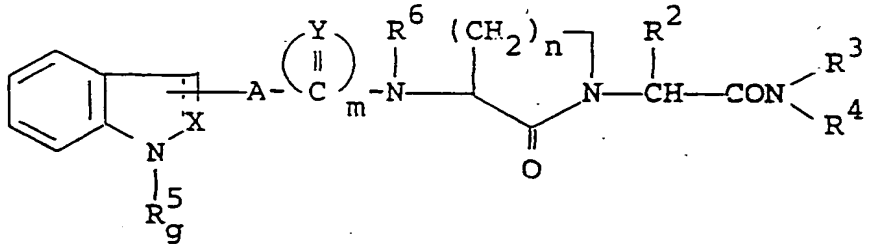
(I-h)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above, and

$R^5_f$ is [2-lower alkyl-3-cyanoisothioureido]-(lower)alkyl,

or a salt thereof, with lower alkylamine,

to give a compound of the formula :



(I-i)

wherein $R^2$, $R^3$, $R^4$, $R^6$, A, X, Y, m and n are each as defined above, and

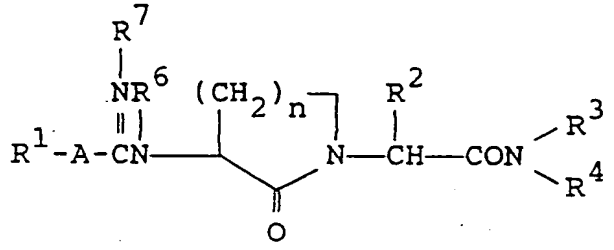
$R^5_g$ is [3-lower alkyl-2-cyanoguanidino]-(lower)alkyl,

or a salt thereof.

(7) reacting the compound (I-a) or a salt thereof, with compound of the formula (V) :

$$R^7NH_2 \qquad (V)$$

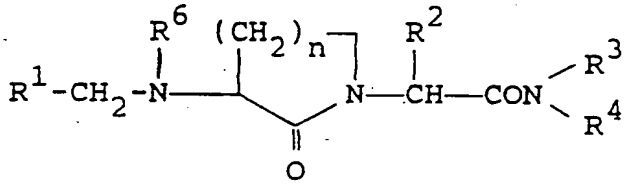
wherein $R^7$ is hydrogen or lower alkyl,
or a salt thereof, to give a compound of the formula :



(I-j)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $R^7$, A, and n are each as defined above,
or a salt thereof, or

(8) subjecting the compound (II) or its reactive derivative at the amino group, or a salt thereof, to Mannich reaction, to give a compound of the formula :



(I-k)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^6$ and n are each as defined above,
or a salt thereof.

5. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

6. A method for treating or preventing Tachykinin-mediated diseases, which comprises administering a compound of claim 1 or pharmaceutically acceptable salt there of to human being or animals.

7. Use of a compound of claim 1 or pharmaceutically acceptable salt thereof as a medicament.

8. Use of compound of claim 1 or pharmaceutically acceptable salt thereof as Tachykinin antagonist.

9. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or pharmaceutically acceptable salt thereof with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 93/00002

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/02; C07K5/06; C07K5/08; A61K37/02

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| A | EP,A,0 360 390 (GLAXO GROUP LIMITED) 28 March 1990 see page 8, line 4 - page 9, line 19; claims | 1,5,7-9 |
| A | EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO., LTD.) 31 October 1990 see claims; examples 51-2 | 1-3,5, 7-9 |
| A | EP,A,0 443 132 (FUJISAWA PHARMACEUTICAL CO., LTD.) 28 August 1991 see claims | 1-3,5, 7-9 |

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 02 APRIL 1993 | 21. 04. 93. |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | FUHR C.K.B. |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | JOURNAL OF MEDICINAL CHEMISTRY<br>vol. 34, no. 10, October 1991, WASHINGTON<br>US<br>pages 3036 - 3043<br>J. SAMANEN ET AL 'An Investigation of Angiotensin II agonist and Antagonist Analogues with 5,5-Dimethylthiazolidine-4-carboxylic Acid and Other Constrained Amino Acids'<br>see page 3041, left column, paragraph 2 -last paragraph<br>----- | 1 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 93/00002

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 6 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

JP 9300002
SA 68164

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/04/93

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0360390 | 28-03-90 | JP-A- | 2124887 | 14-05-90 |
| | | US-A- | 5166136 | 24-11-92 |
| EP-A-0394989 | 31-10-90 | JP-A- | 3027399 | 05-02-91 |
| | | US-A- | 5164372 | 17-11-92 |
| EP-A-0443132 | 28-08-91 | AU-A- | 6801090 | 27-06-91 |
| | | CN-A- | 1064080 | 02-09-92 |
| | | JP-A- | 4210996 | 03-08-92 |